# *C*-BENZOTRAZOLATED NITRONES AS USEFUL SYNTHONS FOR THE SYNTHESIS OF 2,3-DISUBSTITUTED ISOXAZOL-5-ONES

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A new and general method for preparation of C-benzotriazolated nitrones is reported. The reactivity of C-benzotriazolated nitrones is applied for reaction with Reformatsky reagent in the absence of Lewis acid to produce 2,3-Disubstituted isoxazol-5-ones in good yields.

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## Introduction

The chemistry and properties of nitrones **I** have been investigated for more than one century, and their reactivity as electrophiles towards organometallic reagents and as 1,3-dipolar reagents have been long investigated. Nowadays, these reactions are employed abundantly and nitrones have become useful intermediates in synthetic applications.

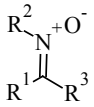


**Figure 1.** Structure of nitrones

The most convenient approach for the generation of nitrones is condensation between hydroxylamines and an aldehyde or a ketone,[1,2] other methods also exist such as oxidation of tertiary hydroxylamines, alkylation of oximes with alkyl halides or oxidation of imine.[3]

There are several reports on nucleophilic additions to nitrones.[4,5] The presence of the C=N moiety in nitrones gives the functionality an iminium character, which is responsible for its reactivity as electrophile with organometallic reagents. Many of these reactions are catalyzed by Lewis acids but strong binding of nitrones to the catalyst is a serious problem as the dipoles have a tendency to form inactive dipole/Lewis acid complexes.[6-16]

Isoxazol-5-ones are useful synthetic intermediates for the preparation of heterocyclic compounds, and important framework in biological systems exhibiting pharmacological activity.[17,18] The preparation of tri-,[19-22] 2,4-di-,[23-26] and 3,4-disubstituted[27-29] isoxazol-5-ones is well documented. By contrast limited literature is available for the preparation of 2,3-disubstituted isoxazol-5-ones although these are important synthetic precursors for pyridines and pyrroles,[30,31] oxazoles,[32] and thiazoles.[33] 2,3-Disubstituted isoxazol-5-ones were previously prepared (i) by reactions of hydroxylamine with β-keto esters,[34-36] but unsymmetrical β-keto esters can form two isomeric isoxazoles, often not easily separable or (ii) by reactions of diketene with hydroxylamines or sulfonylhydroxamic acids, but the starting materials are not easily available[37,38] or (iii) by acylation of 3-substituted isoxazol-5-ones with aroyl chlorides; although acylation frequently gives a mixture of *N*-aroyl and *O*-aroyl derivatives.[39] Thus previous reports for the preparation of 2,3-disubstituted isoxazol-5-ones have drawbacks including lack of generality, unavailability of starting materials, low yields and selectivity.

Continuing the ongoing interest in the study of the reactivity of benzotiazolated derivatives and its application for the synthesis of heterocycles, an easy preparation of *C*-benzotriazolated nitrones **3** and the conversion of **3** into 2,3-disubstituted isoxazol-5-ones **6** in the absence of Lewis acid is now described.

## Results and Discussion

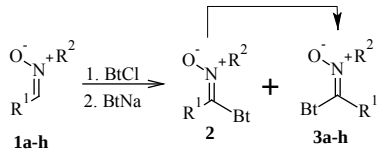
Diaryl(heteroaryl) nitrones **1a-h** were prepared following literature procedures (i) from a hydroxylamine and an aldehyde or (ii) by imine oxidation.[40-42] Treatment of **1a-h** with *N*-chlorobenzotriazole (BtCl) and sodium benzotriazolate (BtNa) in THF furnished exclusively **3a-h** in 73-81 % overall yields. Initial formation of **3** was demonstrated by the reaction of *C*,*N*-di(4-methylphenyl)nitrone **1a** with chlorobenzotriazole and sodium benzotriazolate in THF for 4 hours which gave a mixture separated by column chromatography into **2a** (40 %) and **3a** (35 %). However, when the reaction mixture was heated at reflux temerature for 3 hours, only isomer **3a** was obtained in 73 % yield; presumably due to the conversion of the kinetic product **2a** to the more stable thermodynamic product **3a** (Scheme 1).

The Reformatsky reagent **5** was prepared from ethylbromoacetate (**4**) and zinc after its activation with trimethylsilylchloride.

**Table 1.** Synthesis of **3**.

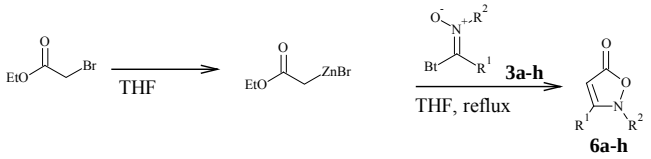
| Starting materials | | | | Products | | | | |
|---|---|---|---|---|---|---|---|---|
| **1** | m.p. (°C) | Lit. m.p. (°C) | Reference | **3** | $R^1$ | $R^2$ | Yield (%)[a] | m.p. (°C) |
| **a** | 129-130 | 129-130 | 43 | **a** | 4-$CH_3C_6H_4$ | 4-$CH_3C_6H_4$ | 77 | 140-141 |
| **b** | 111-113 | 114 | 44 | **b** | $C_6H_5$ | $C_6H_5$ | 81 | 131-133 |
| **c** | 116-117 | 116-117 | 44 | **c** | 4-$CH_3OC_6H_4$ | $C_6H_5$ | 81 | 154-156 |
| **d** | 169-170 | -[b] | 45 | **d** | 4-$CH_3OC_6H_4$ | 4-$ClC_6H_4$ | 79 | 131-133 |
| **e** | 141-143 | -[b] | 46 | **e** | 4-$CH_3OC_6H_4$ | $CH_3OC_6H_4$ | 80 | 165-167 |
| **f** | 108-109 | 109 | 47 | **f** | 2-Furyl | $C_6H_5$ | 75 | 128-129 |
| **g** | 87-89 | -[b] | 48 | **g** | 2-Thienyl | $C_6H_5$ | 76 | 183-185 |
| **h** | 89-91 | 88-89 | 49 | **h** | 3-Pyridyl | $C_6H_5$ | 73 | 153-155 |

[a] Isolated yield. [b] Melting point not reported.




**Scheme 1.** C-benzotriazolated nitrones

Treatment of **3a-h** with Reformatsky reagent **5** at reflux temperature for 3 hours afforded exclusively the isoxazol-5-ones **6a-h** in 72-81 % overall yields after purification by column chromatography (Scheme 2, Table 2).




**Scheme 2.** Synthesis of isoxazol-5-ones

**Table 2.** Synthesis of isoxazol-5-ones **6**.

| Entry | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|
| 6a | 4-$CH_3C_6H_4$ | 4-$CH_3C_6H_4$ | 77 |
| 6b | $C_6H_5$ | $C_6H_5$ | 81 |
| 6c | 4-$CH_3OC_6H_4$ | $C_6H_5$ | 79 |
| 6d | 4-$CH_3OC_6H_4$ | 4-$ClC_6H_4$ | 72 |
| 6e | 4-$CH_3OC_6H_4$ | 4-$CH_3OC_6H_4$ | 76 |
| 6f | 2-Furyl | $C_6H_5$ | 78 |
| 6g | 2-Thienyl | $C_6H_5$ | 73 |
| 6h | 3-Pyridyl | $C_6H_5$ | 80 |

The structure of **3a-h** and **6a-h** were all supported by $^1H$, $^{13}C$ NMR spectroscopy, elemental analysis and HRMS.

## Experimental

Melting points were determined on a capillary point apparatus equipped with a digital thermometer. NMR spectra were recorded in $CDCl_3$ or DMSO-$d_6$ with TMS for $^1H$ (300 MHz) and $^{13}C$ (75 MHz) as the internal reference. Column chromatography was performed on silica gel 200–425 mesh. Nitrones **1a-h** were prepared according to literature procedure,[40-42] and the melting points are in accordance with literature data (Table 1).[43-49]

**General procedure for preparation of 3**

Chlorobenzotriazole (0.77 g, 5 mmol) was added to a stirred mixture of nitrone (4 mmol) and sodium benzotriazolate (0.74 g, 5 mmol) in THF (50 mL) at room temperature. The mixture was stirred at reflux temperature for 3 h. Diethyl ether was added and the mixture was filtered. The filtrate was evaporated and the residue was dissolved in diethyl ether, washed with saturated aqueous potassium carbonate, dried over magnesium sulfate and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (eluent: *n*-hexane/ethyl acetate = 2/1).

***N*-[(1*H*-Benzotriazol-1-yl)-(4-methylphenyl)methylene]-4-methylbenzenamine oxide (3a)**

Yield 1.1 g (77 %); pale-yellow microcrystal; mp: 140-141 °C; $^1H$ NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.39 (s, 3H), 6.89 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.44-7.49 (m, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 21.0, 21.7, 109.4, 120.4, 122.2, 124.7, 126.5, 127.8, 129.2, 129.3, 129.4, 134.1, 137.2, 139.7, 142.5, 144.5, 144.9. Anal. Cald for $C_{21}H_{18}N_4O$: C, 73.67; H, 5.30; N, 16.36. Found: C, 73.91; H, 5.33; N, 16.18.

***N*-[(1*H*-Benzotriazol-1-yl) phenylmethylene]benzeneamine oxide (3b)**

Yield 1.0 g (81 %); pale-yellow microcrystal; mp: 131-133 °C; $^1H$ NMR ($CDCl_3$) δ 7.06-7.18 (m, 3H), 7.24-7.53 (m, 8H), 7.90-8.06 (m, 3H); $^{13}C$ NMR ($CDCl_3$) δ 109.3, 120.4, 122.4, 124.8, 127.8, 128.7, 128.8, 129.1, 129.2, 129.6, 131.8, 134.0, 137.3, 145.0, 146.7; HRMS Cald for $C_{19}H_{14}N_4O$ $[M+Na]^+$ : 337.1060. Found: 337.1090.

***N*-[(1*H*-Benzotriazol-1-yl)-(4-methoxyphenyl)methylene]benzenamine oxide (3c)**

Yield 1.11 g (81%); pale-brown microcrystal; mp: 154-156 °C; $^1H$ NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.87-6.97 (m, 2H), 7.07-7.15 (m, 3H), 7.28-7.42 (m, 4H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.92-8.05 (m, 3H); $^{13}C$ NMR ($CDCl_3$) δ 55.5, 109.4, 114.1, 120.4, 121.8, 122.5, 124.8, 128.8, 129.2, 129.5, 130.1, 134.0, 144.9, 146.5, 162.1. Anal. Cald for $C_{20}H_{16}N_4O_2$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.41; H, 4.77; N, 16.02.

**_N_-[(1*H*-Benzotriazol-1-yl)-(4-methoxyphenyl)methylene]-4-chlorobenzenamine oxide (3d)**

Yield 1.19 g (79 %); pale-brown microcrystal; mp: 131-133 $^{o}$C; $^{1}$H NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.92 (d, *J* = 9.0 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.22-7.32 (m, 3H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.93 (d, *J* = 9.0 Hz, 2H), 8.04 (d, *J* = 8.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 55.5, 109.2, 114.2, 120.6, 121.5, 124.0, 125.0, 129.0, 129.5, 130.1, 134.0, 135.3, 137.3, 144.9, 145.0, 162.2. Anal. Cald for $C_{20}H_{15}ClN_4O_2$: C, 63.41; H, 3.99; N, 14.79. Found: C, 63.24; H, 4.01; N, 14.62.

**_N_-[(1*H*-Benzotriazol-1-yl)-(4-methoxyphenyl)methylene]-4-methoxybenzenamine oxide (3e)**

Yield 1.20 g (80 %); pale-brown microcrystal; mp: 165-167 $^{o}$C; $^{1}$H NMR ($CDCl_3$) δ 3.64 (s, 3H), 3.85 (s, 3H), 6.58 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 9.0 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 9.3 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 55.3, 55.4, 109.4, 113.8, 114.0, 120.4, 122.0, 123.9, 124.7, 129.2, 130.0, 134.0, 136.8, 139.8, 144.9, 159.8, 161.9. Anal. Cald for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96. Found: C, 66.96; H, 4.90; N, 14.79.

**_N_-[1*H*-Benzotriazol-1-yl)-(2-furyl)methylene]benzenamine oxide (3f)**

Yield 0.912 g (75%); pale-brown microcrystal; mp: 128-129 $^{o}$C; $^{1}$H NMR ($CDCl_3$) δ 6.68-6.74 (m, 1H), 7.11-7.21(m, 3H), 7.25-7.44 (m, 5H), 7.50 (t, *J* = 7.2 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 8.28 (d, *J* = 3.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 109.2, 113.2, 118.3, 120.4, 122.9, 124.7, 128.9, 129.1, 129.2, 130.3, 134.1, 144.1, 144.9, 145.0, 145.3. Anal. Cald for $C_{17}H_{12}N_4O_2$: C, 67.10; H, 3.97; N, 18.41. Found: C, 67.35; H, 4.16; N, 17.95.

**_N_-[(1*H*-Benzotriazol-1-yl)-(2-thienyl)methylene]benzenamine oxide (3g)**

Yield 0.973 g (76%); pale-brown microcrystal; mp: 183-185 $^{o}$C: $^{1}$H NMR ($CDCl_3$) δ 6.77 (d, *J* = 3.6 Hz, 1H), 7.06-7.20 (m, 4H), 7.30-7.36 (m, 3H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 4.8 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 109.2, 120.5, 123.0, 124.9, 127.2, 128.9, 129.5, 130.0, 130.7, 130.8, 131.5, 133.8, 144.2, 144.9. Anal. Cald for $C_{17}H_{12}N_4OS$: C, 63.73; H, 3.78; N, 17.49. Found: C, 63.48; H, 3.73; N, 17.33.

**_N_-[(1*H*-Benzotriazol-1-yl)-(3-pyridyl)methylene]benzenamine oxide (3h)**

Yield 0.792 g (73%); pale-brown microcrystal; mp: 153-155 $^{o}$C; $^{1}$H NMR ($CDCl_3$) δ 7.08-7.22 (m, 3H), 7.26-7.35 (m, 3H), 7.37-7.43 (m, 2H), 7.51 (t, *J* = 7.7 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 8.51-8.55 (m, 1H), 8.69 (d, *J* = 4.4 Hz, 1H), 8.91 (d, *J* = 1.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 109.0, 120.7, 122.4, 123.4, 125.1, 125.9, 128.9, 129.6, 130.0, 133.8, 134.6, 143.3, 145.0, 146.3, 148.6, 151.7; HRMS Cald for $C_{18}H_{13}N_5O$ $[M+Na]^+$ : 338.1012. Found: 338.1036.

**General procedure for preparation of 6**

Trimethylsilyl chloride (0.04 mL) was added to a suspension of zinc (0.5 g, 7.7 mmol) in THF at room temperature and the mixture was stirred under reflux for 30 min. To the cooled reaction mixture was added ethyl bromoacetate (2.5 mmol) and the suspension was stirred for 1 h at room temperature followed by addition of **3** (1 mmol) dissolved in THF (1 mL). The reaction mixture was heated to reflux for 3 h and cooled to room temperature. The mixture was filtered, concentrated under reduced pressure and residue subjected to column chromatography on silica gel using ethyl acetate/hexane (1:3) to give **6**.

**2,3-Di(4-methylphenyl)isoxazol-5-one (6a)**

Yield 0.204 g (77%); pale yellow microcrystals; mp: 166.0-168.0 $^{o}$C; $^{1}$H NMR (DMSO-$d_6$) δ 2.28 (s, 3H), 2.38 (s, 3H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.88 (d, *J* = 7.5 Hz, 2H), 10.09 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 20.5, 21.0, 120.4, 127.7, 128.9, 129.0, 132.2, 132.5, 136.8, 141.4, 165.2. HRMS Cald for $C_{17}H_{15}NO_2$ $[M+H]^+$-$H_2O$: 248.1075. Found: $[M+H]^+$-$H_2O$: 248.1024.

**2,3-Diphenylisoxazol-5-one (6b)**

Yield 0.192 g (81%); pale yellow microcrystals; mp: 152.0-154.0 $^{o}$C; $^{1}$H NMR (DMSO-$d_6$) δ 7.10 (t, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.49-7.64 (m, 3H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 10.26 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 120.4, 123.7, 127.7, 128.4, 128.6, 131.6, 135.0, 139.2, 165.6. HRMS Cald for $C_{15}H_{11}NO_2$ $[M+H]^+$-$H_2O$: 220.0762. Found: $[M+H]^+$-$H_2O$ 220.0711.

**3-(4-Methoxyphenyl)-2-phenylisoxazol-5-one (6c)**

Yield 0.211 g (79%); pale yellow microcrystals; mp: 160.0-162.0 $^{o}$C; $^{1}$H NMR (DMSO-$d_6$) δ 3.84 (s, 3H), 7.02-7.12 (m, 3H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.77 (d, *J* = 7.8 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H), 10.09 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 55.5, 113.6, 120.3, 123.4, 127.0, 128.6, 129.6, 139.4, 161.9, 164.9. HRMS Cald for $C_{16}H_{13}NO_3$ $[M+H]^+$-$H_2O$: 250.0868. Found: $[M+H]^+$-$H_2O$ 250.0817.

**2-(4-Chlorophenyl)-3-(4-methoxyphenyl)isoxazol-5-one (6d)**

Yield 0.217 g (72%); yellow microcrystals; mp: 191.0 - 193.0 $^{o}$C; $^{1}$H NMR (DMSO-$d_6$) δ 3.84 (s, 3H), 7.07 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 8.7 Hz, 2H), 7.96 (d, *J* = 9.0 Hz, 2H), 10.21 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 55.4, 113.6, 121.8, 126.7, 127.0, 128.5, 129.7, 138.4, 162.0, 165.0. HRMS Cald for $C_{16}H_{12}ClNO_3$ $[M+H]^+$-$H_2O$: 284.0478. Found: $[M+H]^+$-$H_2O$ 284.0427.

**2,3-Di(4-methoxyphenyl)isoxazol-5-one (6e)**

Yield 0.226 g (76%); yellow microcrystals; mp: 188.0-190.0 $^{o}$C; $^{1}$H NMR (DMSO-$d_6$) δ 3.74 (s, 3H), 3.83 (s, 3H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 9.97 (s, 1H);

$^{13}$C NMR (DMSO-$d_6$) δ 55.2, 55.4, 113.6, 113.7, 122.0, 127.1, 129.5, 132.4, 155.4, 161.8, 164.5. HRMS Cald for $C_{17}H_{15}NO_4$ $[M+H]^+$-$H_2O$: 280.0973. Found: $[M+H]^+$-$H_2O$ 280.0925.

**3-(2-Furyl)-2-phenylisoxazol-5-one (6f)**

Yield 0.177 g (78%); yellow microcrystals; mp: 148.0-150.0 °C; $^1$H NMR (DMSO-$d_6$) δ 7.10-7.20 (m, 3H), 7.24-7.40 (m, 2H), 7.53 (t, $J$ = 7.2 Hz, 1H), 8.00 (t, $J$ = 8.1 Hz, 1H), 8.38 (d, $J$ = 3.9 Hz, 1H), 10.12 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 119.9, 122.3, 124.7, 134.4, 148.2, 149.5, 153.1, 165.5. Anal. Cald for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.16. Found: C, 68.65; H, 4.01; N, 6.22

**2-Phenyl-3-(2-thienyl)isoxazol-5-one (6g)**

Yield 0.178 g (73%); yellow microcrystals; mp: 143.0-145.0 °C; $^1$H NMR (DMSO-$d_6$) δ 7.06-7.22 (m, 3H), 7.30-7.36 (m, 2H), 7.40 (d, $J$ = 7.2 Hz, 1H), 7.49 (t, $J$ = 7.4 Hz, 2H), 7.67 (d, $J$ = 4.8 Hz, 1H), 10.16 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 124.6, 136.5, 137.2, 137.4, 137.6, 138.5, 139.6, 143.5, 145.8, 148.2, 164.4. Anal. Cald for $C_{13}H_9NO_2S$: C, 64.18; H, 3.73; N, 5.76. Found: C, 64.24; H, 3.65; N, 5.92

**2-Phenyl-3-(3-pyridyl)isoxazol-5-one (6h)**

Yield 0.190 g (80%); yellow microcrystals; mp: 182.0-184.0 °C; $^1$H NMR (DMSO-$d_6$) δ 7.08-7.22 (m, 3H), 7.37-7.43 (m, 1H), 7.51 (t, $J$ = 7.7 Hz, 1H), 8.03 (d, $J$ = 8.4 Hz, 1H), 8.51-8.55 (m, 1H), 8.69 (d, $J$ = 4.4 Hz, 1H), 8.91 (d, $J$ = 1.8 Hz, 2H), 10.21 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 124.7, 134.3, 137.4, 137.6, 138.6, 143.6, 146.7, 148.3, 149.2, 149.5, 159.0, 163.3. Anal. Cald for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.41; H, 4.11; N, 11.65.

## Conclusion

In summary novel *N*-substituted *C*-benzotriazolated nitrones were synthesized in good yields. The reactivity of nitrones was studied with Reformatsky reagent providing a new approach to 2,3-disubstituted isoxazol-5-ones without using Lewis acid.

## References


[1]Merino, P., Franco, S., Merchan, F. L., Tejero, T., *Tetrahedron:Assymetry,* **1997**, *8*, 3489.

[2]Borch, R. F., Bernstein, M. D., Durst, H. D., *J. Am. Chem. Soc*., **1971**, 2897.

[3]Christenen, D., Jorgensen, K. A., *J. Org. Chem.* **1989**, 54, 126

[4]Merino, P., Franco, S., Merchan, F. L., Tejero, T., *Synlett,* **2000**, 442.

[5]Lombardo, M., Trombini, C. *Synthesis*, **2000**, 759.

[6]Cardona, F., Goti, A., *Angew. Chem. Int. Ed.,* **2005**, *44*, 7832.

[7]Palomo, C., Oiarbide, M., Areco, E., Garcia, J. M., Lopez, R., Gonzalez, A., Linden, A., *Angew. Chem. Int. Ed.,* **2005**, *44*, 6187.

[8]Gothelf, K. V., Jørgensen, K. A., *J. Org. Chem.,* **1994**, *59*, 5687.

[9]Hori, K., Kodama, H., Ohta, T., Furukawa, I. *Tetrahedron Lett.,* **1996**, *37*, 5947.

[10]Jensen, K., Gothelf, K. V., Hazell, R. G., Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471.

[11]Kobayashi, S., Kawamura, M. *J. Am. Chem. Soc.,* **1998**, *120*, 5840.

[12]Hori, K., Kodama, H., Ohta, T., Furukawa, I. *J. Org. Chem.,* **1999**, *64*, 5017.

[13]Desimoni, G., Faita, G., Mortoni, A., Righetti, P., *Tetrahedron Lett.* **1999**, *40*, 2001.

[14]Iwasa, S., Tsushima, S., Shimada, T., Nishiyama, H., *Tetrahedron Lett.,* **2001**, *42*, 6715.

[15]Shirahase, M., Kanemasa, S., Oderaotoshi, Y. *Org. Lett.,* **2004**, *6*, 675.

[16]Dugovič, B., Fišera, L., Hametner, C., Prónayová, N., *ARKIVOC,* **2003**, *14*, 162.

[17]Laufhlin, S. K., Clark, M. P., Djungn J. F., Golebiowski, A., Brugel, T. A., Sabat, M., Bookland, R. G., Laufersweiler, M. J., VanRens, J. C., Townes, J. A., De, B., Hsieh, L. C., Xu, S. C., Walter, R. L., Mekel, M. J., Janusz, M. J., *Bioorg. Med. Chem. Lett*., **2005**, *15*, 2399.

[18]Ikegami, F., Yamamoto, A., Sekine, T., Ishikawa, T., Kusamae-Eguch, K., Kusama, T., Watanabe, K., *Chem. Pharm. Bull.,* **2000**, *48*, 278.

[19]Khalafy, J., Ebrahimlo, A. R. M., Eisavi, R., Dilmaghani, A., *ARKIVOC,* **2005**, (*xiv*), 59.

[20]Abbiati, G., Beccalli, E. M., Broggini, G., Zoni, C., *Tetrahedron,* **2003**, *59*, 9887.

[21]Prager, R. H., Smith, J. A., *J. Chem. Soc. Commun.,* **1994**, 1805.

[22]Chidichimo, G., Cum, G., Lelj, F., Sindona, G., Uccella, N., *J. Am. Chem. Soc.,* **1980**, *102*, 1372.

[23]Tamura, M., Ise, Y., Okajima, Y., Nishiwaki, N., Ariga, M., *Synthesis,* **2006**, 3453.

[24]Quesnelle, C. A., Gill, P., Roy, S., Dodier, M., Marinier, A., Martel, A., Snyder, L. B., D'Andrea, S. V., Bronson, J. J., Frosco, M., Beaulieu, D., Warr, G. A., DenBleyker, K. L., Stickle, T. M., Yang, H., Chaniewski, S. E., Ferraro, C. A., Taylor, D., Russell, J. W., Santone, K. S., Clarke, J., Drain, R. L., Knipe, J. O., Mosure, K., Barrett, J. F., *Bioorg. Med. Chem. Lett.,* **2005**, *15*, 2728,

[25]Beccalli, E. M., Marchesini, A., *Tetrahedron,* **1997**, *53*, 10433.

[26]Ang, K. H., Prager, R. H. *Tetrahedron* **1992**, *48*, 9073.

[27]Khalafy, J., Marjani, A. P., Ebrahimlo, A. R. N., *J. Braz. Chem. Soc.,* **2006**, *17*, 570.

[28]Nenajdenko, V. G., Zakurdaev, E. P., Gololobov, A. M., Balenkova, E. S., *Russ. Chem. Bull., Int. Ed.,* **2005**, *54*, 220.

[29]Batra, S., Bhaduri, A. P., *J. Indian Inst. Sci.,* **1994**, *74*, 213.

[30]Cox, M., Dixon, M., Lister, T., Prager, R. H., *Aust. J. Chem.*, **2004**, *57*, 455.

[31]Cox, M., Prager, R. F., Riessen, D. M., *ARKIVOC,* **2001**, (*vii*), 88.

[32]Clark, A. D., Ha, U. T., Prager, R. H., Smith, J., *Aust. J. Chem.,* **1999**, *52*, 1029.

[33]Millan, D. S., Prager, R. H., *J. Chem. Soc., Perkin Trans. 1,* **1998**, 3245.

[35]Sasaki, T., Hayakawa, K., Nishida, S., *J. Chem. Soc. Commun.*, **1980**, 1054.

[35]Sarlo, F. D., Fabbrini, L., Renzi, G., *Tetrahedron,* **1996**, *22*, 2989.

[36]Saeki, S., Honda, H., Hamana, M., *Chem. Chem. Pharm. Bull.,* **1983**, *31*, 1474.

[37]Fujimoto, M., Sakai, M., *Chem. Pharm. Bull.,* **1965**, *13*, 248.

[38]Katritzky, A. R., Øksne, S., Boulton, A. J., *Tetrahedron,* **1962**, *18*, 777.

[39]Sato, K., Ueda, T., Sugai, S., *Chem. Pharm. Bull.* **1986**, *34*, 3153.

[40]Merino, P., Franco, S., Merchan, F. L., Tejero, T., *Tetrahedron:Asymmetry,* **1997**, *8*, 3489.

[41]Borch, R. F., Bernstein, M. D., Durst, H. D., *J. Am. Chem. Soc*., **1971**, *93*, 2897.

[42]Christenen, D., Jorgensen, K. A., *J. Org. Chem*., **1989**, *54*, 126.

[43]Rosenberg, H. M., Jorgensen, K. A., *J. Org. Chem*., **1972**, *37*, 1443.

[44]Tian, L., Xu, G. –Y., Liu, L.–Z., *Synthesis,* **2003**, 1329.

[45]Singh, N., Sethi, P. S., *Indian J. Chem.,* **1975**, *13*, 990.

[46]Dutta, D. K.; Boruah, R. C.; Sandhu, J. S. *Indian J. Chem., Sect. B.,* **1986**, *25B*, 350.

[47]Singh, J., Ishar, M. P. S., Girghar, N. K., Singh, L. *J. Heterocycl. Chem.,* **2005**, *42*, 1047.

[48]Liotta, D., Baker, A. D., Goldman, N. L., Weinstein-Lanse, F., Felsen-Reingold, D., Engel, R., *J. Org. Chem.,* **1974**, *39*, 1974.

[49]Lo, M. M. –C.; Fu, G. C., *J. Am. Chem. Soc.,* **2002**, *124*, 45, 4572.

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