New reaction of cyclic nitronates: C,C-cross coupling with silyl enolates

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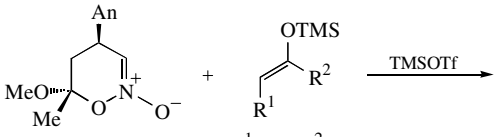
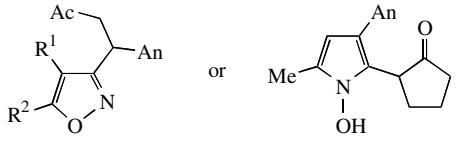
The interaction of cyclic nitronate esters with silyl enolates in the presence of trimethylsilyl triflate leads to the formation of five-membered heterocycles, isoxazoles or *N*-hydroxypyrrol.

Six-membered cyclic nitronates (*e.g.*, **1**, Scheme 1), which are readily available *via* the [4 + 2] cycloaddition of nitroalkenes to alkenes are widely used for the diastereoselective synthesis of various products mainly as 1,3-dipoles in [3 + 2] cycloaddition reactions.[1,2] However, we believe that the synthetic utility of these interesting nitronic acids derivatives can be expanded.



1
An = 4-MeOC$_6$H$_4$
OTf = OSO$_2$CF$_3$
TMS = Me$_3$Si

2a R^1 = H, R^2 = Me
2b R^1 = H, R^2 = An
2c R^1,R^2 = –(CH$_2$)$_4$–
2d R^1,R^2 = –(CH$_2$)$_3$–



3a 54%
3b 62%
3c 65%

4d 61%

Scheme 1

Here, we describe a new reaction of model nitronate **1**† with silyl enolates **2a–d** in the presence of trimethylsilyl triflate (TMSOTf), which results in the formation of a new C–C bond (Scheme 1). The final product of this transformation depends on the structure of silyl enolate. The interaction of nitronate **1** with alkenes **2a–c** gives rise to isoxazoles **3a–c**, while with a slightly modified silyl enolate **2d** (*cf.* **2d** and **2c**) it furnishes *N*-hydroxypyrrol **4d** (Scheme 1).‡

The reactions presented in Scheme 1 are not typical of the chemistry of nitronate esters. A plausible mechanism for this transformation is shown in Scheme 2.

The initial step is the interaction of substrate **1** with TMSOTf, which yields cationic species **A**. This species reacts with silyl enolates as a carbon electrophile to produce *N*-siloxyoxazines **B** (five-membered analogues of **B**, *N*-siloxyisoxazolidines, are well-known products of the [3 + 2] cycloaddition of silylnitronates to alkenes[4]). At the next step, intermediates **B** undergo the TMSOTf-induced fragmentation resulting in the formation of 3-nitroso-1,6-diketone derivative **C**.§ The isomerisation of a nitroso group into an oxime moiety followed by the intramolecular interaction of the oximino function with one of the two keto groups furnishes the final adducts, isoxazoles **3a–c** or *N*-hydroxypyrrol **4d**, respectively.

An alternative route leading to the formation of *N*-hydroxypyrrol **4** becomes favourable only for the reaction involving 1-trimethylsiloxycyclopentene **2d** since, in this case, the formation of an isoxazole derivative should imply the closure of a sterically hindered fused 5,5-bicyclic ring system.

The necessity of using an excess of TMSOTf in the sequence of transformations is obviously due to the quenching of this Lewis acid by water formed as a result of the aromatisation of oxime **D** into products **3a–c** and **4d**.

The structures of compounds **3a–c** and **4d** were supported by the consistent results of elemental analysis and ^{1}H and ^{13}C NMR, IR spectroscopy and mass spectrometry.¶

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† Previously unknown nitronate **1** was prepared as a single *trans*-isomer by a slightly modified published procedure:[3] $SnCl_4$ (0.70 ml, 6 mmol) was added to a stirred solution of 1-methoxy-4-[(*E*)-2-nitroethenyl]benzene (895 mg, 5 mmol) in CH_2Cl_2 (25 ml) at –78 °C. After stirring for 5 min, the reaction mixture was cooled down to –94 °C, and 2-methoxypropene (0.91 ml, 9.5 mmol) was added. The reaction mixture was stirred for 5 min and then poured into a mixture of a saturated aqueous solution of $NaHCO_3$ (25 ml) and EtOAc (75 ml). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×25 ml). Combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (25 ml) and brine (25 ml), dried over Na_2SO_4 and evaporated. The residue was recrystallised from Et_2O to give 1.11 g (88%) of the analytically pure product.

‡ General procedure for the preparation of **3a–c** and **4d**: Silylenolate R^{2}C(OSiMe$_3$)=CHR^1 (3.5 mmol) and TMSOTf (0.47 ml, 2.5 mmol) were added to a stirred solution of 1,2-oxazine-*N*-oxide **1** (252 mg, 1 mmol) in CH_2Cl_2 (5 ml) at –30 °C. The reaction mixture was stirred at –30 °C (for 24 h, **3a**; for 30 min, **3b**; for 18 h, **3c** or for 5 days, **4d**), a solution of $Et_3NBn^+Cl^-$ (690 mg, 3.0 mmol) in CH_2Cl_2 (5 ml) was added and the temperature was allowed to reach ambient. Then, it was poured into a mixture of a saturated aqueous solution of $NaHCO_3$ (10 ml) and Et_2O (20 ml). The organic layer was separated (water can be added to facilitate the separation of layers) and the aqueous layer was back extracted with diethyl ether (2×10 ml). Combined organic layers were washed successively with a saturated aqueous $NaHCO_3$ solution (20 ml) and brine (20 ml), dried over Na_2SO_4 and evaporated in a vacuum. The residue was subjected to column chromatography (silica gel, EtOAc–hexane 1:5 → 1:1) and recrystallised from Et_2O (for **3a**, **3b** and **4d**) or distilled in a short-path apparatus (for **3c**) to give analytically pure products: **3a**, 140 mg (54%); **3b**, 218 mg (62%); **3c**, 194 mg (65%); **4d**, 174 mg (61%).

§ Related fragmentation was observed earlier for *N*-siloxyisoxazolidines[5,6] under the action of nucleophiles.

¶ Some characteristics of heterocycles **3a–c** and **4d** (NMR spectra were recorded in $CDCl_3$ on a Bruker AM 300 spectrometer at 300.31 and 75.47 MHz for ^1H and ^{13}C, respectively; TMS was an internal standard. IR spectra were recorded on a Bruker VECTOR 22 instrument. Mass spectra were recorded on a Kratos MS-30 instrument).

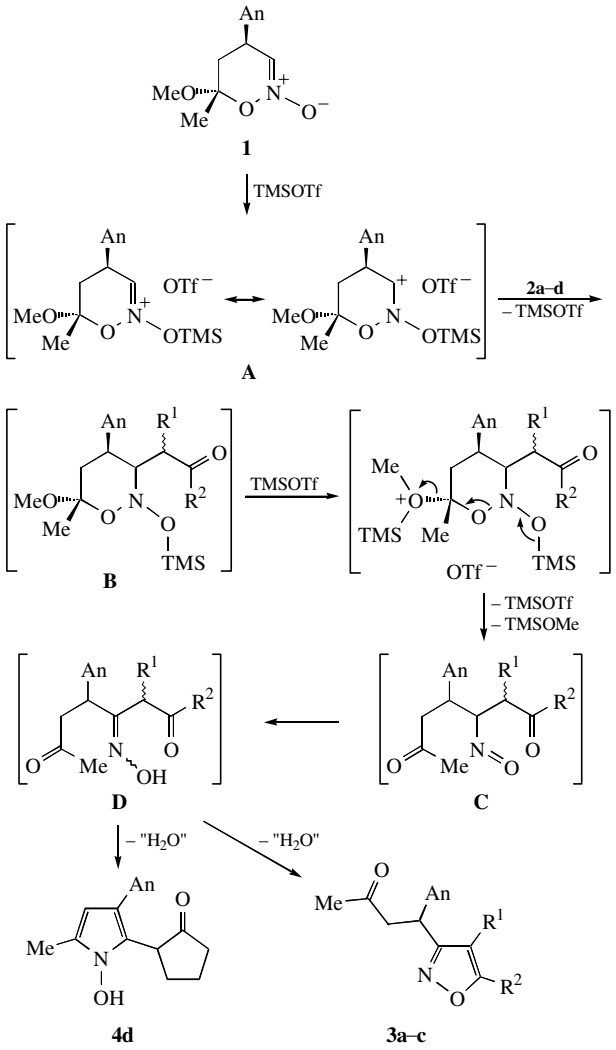
5,6-Dihydro-6-methoxy-4-(4-methoxyphenyl)-6-methyl-4H-1,2-oxazine-2-oxide **1**: mp 122–123 °C (Et_2O). ^1H NMR, δ: 1.56 (s, 3H, Me), 1.84 (t, 1H, CH_2, J 12.9 Hz), 2.27 (dd, 1H, CH_2, ^2J 12.9 Hz, ^3J 6.9 Hz), 3.50 (s, 3H, OMe), 3.82 (s, 3H, C_6H_4–OMe), 3.97 (ddd, 1H, CHAn, $^3J \approx 13$ Hz, ^3J 6.9 Hz, ^3J 2.6 Hz), 6.38 (d, 1H, CH=N, ^3J 2.6 Hz), 6.89 (d, 2H, 3-H_{An}, ^3J 8.3 Hz), 7.14 (d, 2H, 2-H_{An}, ^3J 8.3 Hz). ^{13}C NMR, δ: 20.9 (Me), 36.8 (CHAn), 38.2 (CH_2), 50.0 (OMe), 55.3 (AnOMe), 104.8 (CH=N), 114.5 ($CH_{3\text{-}An}$), 128.6 ($CH_{2\text{-}An}$), 131.4 ($CH_{1\text{-}An}$), 159.1 ($CH_{4\text{-}An}$). Found (%): C, 62.25; H, 6.77, N, 5.32. Calc. for $C_{13}H_{17}NO_4$ (%): C, 62.14; H, 6.82; N, 5.57.

4-(4-Methoxyphenyl)-4-(5-methyl-3-isoxazolyl)butan-2-one **3a**: mp 71–72 °C (Et_2O). ^1H NMR, δ: 2.16 (s, 3H, Me), 2.32 (s, 3H, Me), 2.93 (dd, 1H, CH_2C=O, ^2J 17.3 Hz, ^3J 6.4 Hz), 3.48 (dd, 1H, CH_2C=O, ^2J 17.3 Hz, ^3J 8.3 Hz), 3.78 (s, 3H, OMe), 4.52 (dd, 1H, CHAn, ^3J 8.3 Hz, ^3J 6.4 Hz), 5.70 (s, 1H, CH=C), 6.84 (d, 2H, An, ^3J 8.7 Hz), 7.16 (d, 2H, An, ^3J 8.7 Hz). ^{13}C NMR, δ: 12.22 (Me), 30.59 (Me), 38.37 (*C*HAn), 48.16 (CH_2), 55.41 (OMe), 101.67 (*C*H=C), 114.28 and 129.00 ($2CH_{An}$), 133.47 and 158.76 ($2C_{An}$), 165.76 (C=N), 169.32 (CH=*C*), 206.53 (C=O). MS (EI, 70 eV), *m/z* (%): 259 ([M]$^+$, 56), 244 ([M – Me]$^+$, 7), 216 ([M – Ac]$^+$, 100), 202 (48), 174 (52), 159 (35), 143 (18), 133 (60), 119 (30), 108 (17), 103 (19), 91 (40), 77 (35), 71 (38), 65 (27), 51 (15). IR (neat, ν/cm^{-1}): 1720 (s, C=O), 1611 (s), 1513 (s), 1255 (s). Found (%): C, 69.57; H, 6.59; N, 5.25. Calc. for $C_{15}H_{17}NO_3$ (%): C, 69.48; H, 6.61; N, 5.40.

4-(4-Methoxyphenyl)-4-[5-(4-methoxyphenyl)-3-isoxazolyl]butan-2-one **3b**: mp 106–108 °C (Et_2O). ^1H NMR, δ: 2.18 (s, 3H, Me), 2.96 (dd, 1H, CH_2C=O, ^2J 17.1 Hz, ^3J 6.5 Hz), 3.53 (dd, 1H, CH_2C=O, ^2J 17.1 Hz, ^3J 8.3 Hz), 3.77 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.61 (dd, 1H, CHAn, ^3J 8.3 Hz, ^3J 6.5 Hz), 6.10 (s, 1H, CH=C), 6.85 (d, 2H, An, ^3J 8.4 Hz), 6.91 (d, 2H, An, ^3J 8.5 Hz), 7.21 (d, 2H, An, ^3J 8.5 Hz), 7.62 (d, 2H, An, ^3J 8.4 Hz). ^{13}C NMR, δ: 30.57 (Me), 38.41 (*C*HAn), 48.12 (CH_2), 55.30 (OMe), 55.40 (OMe), 98.19 (*C*H=C), 114.26, 114.32, 127.36 and 129.02 ($4CH_{An}$), 120.34, 133.36, 158.71 and 161.03 ($4C_{An}$), 166.14 (C=N), 169.73 (CH=*C*), 206.42 (C=O). IR (neat, ν/cm^{-1}): 1712 (s, C=O), 1617 (s), 1513 (s), 1253 (s). Found (%): C, 71.72; H, 6.04; N, 3.70. Calc. for $C_{21}H_{21}NO_4$ (%): C, 71.78; H, 6.02; N, 3.99.

4-(4-Methoxyphenyl)-4-(4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yl)butan-2-one **3c**: bp 175–179 °C (1 torr). ^1H NMR, δ: 1.70 (m, 5H, $3CH_2$), 2.14 (s, 3H, Me), 2.25 (m, 1H, CH_2), 2.57 (m, 2H, CH_2), 2.88 (dd, 1H, CH_2C=O, ^2J 17.3 Hz, ^3J 6.2 Hz), 3.52 (dd, 1H, CH_2C=O, ^2J 17.3 Hz, ^3J 8.5 Hz), 3.75 (s, 3H, OMe), 4.43 (dd, 1H, CHAn, ^3J 8.5 Hz, ^3J 6.2 Hz), 6.79 (d, 2H, An, ^3J 8.7 Hz), 7.13 (d, 2H, An, ^3J 8.7 Hz). ^{13}C NMR, δ: 19.10, 22.04, 22.21 and 22.56 ($4CH_2$), 30.58 (Me), 37.56 (*C*HAn), 48.01 (CH_2C=O), 55.20 (OMe), 111.65 (*C*=CO), 114.03 and 129.07 ($2CH_{An}$), 132.64 and 158.50 ($2C_{An}$), 162.78 (C=N), 167.95 (C=*C*O), 206.69 (C=O). IR (neat, ν/cm^{-1}): 1717 (s, C=O), 1611 (w), 1512 (s), 1251 (s). Found (%): C, 72.21; H, 7.25. Calc. for $C_{18}H_{21}NO_3$ (%): C, 72.22; H, 7.07.

2-[1-Hydroxy-3-(4-methoxyphenyl)-5-methyl-1H-pyrrol-2-yl]cyclopentanone **4d**: mp 140–144 °C (Et_2O). ^1H NMR, δ: 1.86 (m, 1H, CH_2), 2.12 (m, 2H, CH_2), 2.19 (s, 3H, Me), 2.34 (m, 3H), 3.64 (t, 1H, CHC=O, ^3J 10.3 Hz), 3.82 (s, 3H, OMe), 5.77 (s, 1H, CH=CN), 6.90 (d, 2H, An, ^3J 8.6 Hz), 7.22 (d, 2H, An, ^3J 8.6 Hz), 8.42 (br. s, 1H, NOH). ^{13}C NMR, δ: 10.52 (Me), 21.28, 30.47 and 38.09 ($3CH_2$), 47.62 (*C*HC=O), 55.42 (OMe), 101.57 (*C*H=C), 113.98 and 129.37 ($2CH_{An}$), 118.77, 120.64 and 125.24 (2C–N and NC=*C*), 129.82 and 157.97 ($2C_{An}$), 222.92 (C=O). IR (neat, ν/cm^{-1}): 3284 (br. s, OH), 1725 (s, C=O), 1528 (s), 1243 (s). Found (%): C, 71.59; H, 6.75; N, 5.38. Calc. for $C_{17}H_{19}NO_3$ (%): C, 71.56; H, 6.71; N, 4.91.



Scheme 2