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Stereoselective synthesis of spirocyclic nitronates by $SnCl_4$-promoted reaction of nitroalkenes with C-2 substituted 4-methylidene-1,3-dioxolane

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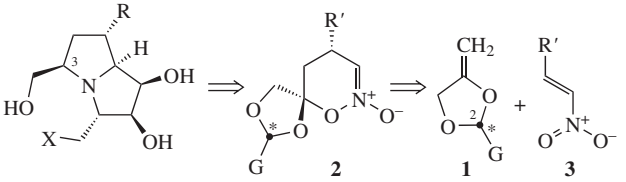
$SnCl_4$-promoted [4+2] cycloaddition of β-nitrostyrenes to 4-methylidene-1,3-dioxolane provides stereoselective synthesis of spirocyclic nitronates. 2-Nitrovinyl benzoate under the same conditions produces δ-substituted nitrodiene as a single *E*,*E*-isomer.

5,6-Dihydro-4*H*-1,2-oxazine-*N*-oxides (six-membered cyclic nitronates) are versatile intermediates in the total synthesis of natural and medicinally relevant molecules.[1] In particular, [3+2]-cycloaddition of nitronates with electron-deficient alkenes followed by reductive cleavage of N–O bonds have proven to be an efficient strategy towards indolizidine and pyrrolizidine alkaloids (Denmark's approach).[2] Our synthetic strategy to the fused pyrrolidines employs transformation of nitronates to C-3 functionalized 5,6-dihydro-4*H*-1,2-oxazines by silylation and the subsequent reduction of the oxime ether group.[3] Chiral auxiliary-equipped nitronates allow one to use such chemistry for obtaining non-racemic materials.[2–5]

In our ongoing project on the synthesis of polysubstituted pyrrolizidines[3(b),6] we became interested in using chiral C-2 substituted 4-methylidene-1,3-dioxolanes **1** as precursors of spirocyclic nitronates **2** (Scheme 1). The latter may be considered as precursors of pyrrolizidine alkaloids with a hydroxymethyl group at C-3, in particular Hyacinthacine B1[7(a)] and the recently discovered Pochonicine.[7(b)] Due to a rigid cyclic structure of vinyl ethers **1** high stereocontrol can be expected in the cycloaddition with nitroalkenes **3**. Methylidenedioxolanes of type **1** are easily available from the corresponding carbonyl compounds and epichlorohydrin.[8] In this context, chiral ketones may serve as a new type of chiral auxiliaries for the preparation of enantiomerically pure nitronates.[8(b)]



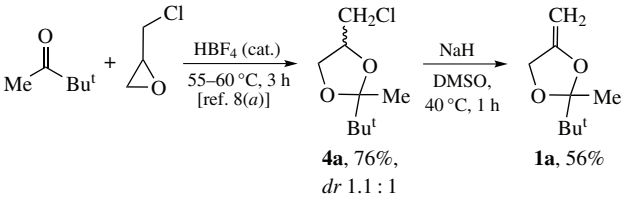
Hyacinthacine B1 (R = H, X = OH)
Pochonicine (R = OH, X = NHAc)

R′ = H, OPG
G = bulky group

Scheme 1

Here we report the application of asymmetrically substituted methylidenedioxolanes **1** for the stereoselective synthesis of previously unknown spirocyclic nitronates **2**. For model studies racemic methylidenedioxolane **1a** bearing sterically distinct methyl and *tert*-butyl groups was chosen. The synthesis of previously unknown **1a** was accomplished in two steps as shown in Scheme 2.[†]

At the first stage, acetalization of *tert*-butyl methyl ketone with epichlorohydrin under acidic catalysis furnished diastereomeric (1.1 : 1) chloromethyldioxolanes **4a** in 76% yield.[8(a)] Treatment of chlorides **4a** with dimsyl sodium gave the desired methylidenedioxolane **1a** in a reasonable yield.



4a, 76%, *dr* 1.1 : 1

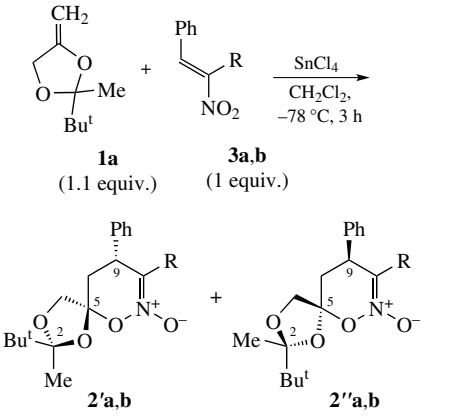
1a, 56%

Scheme 2

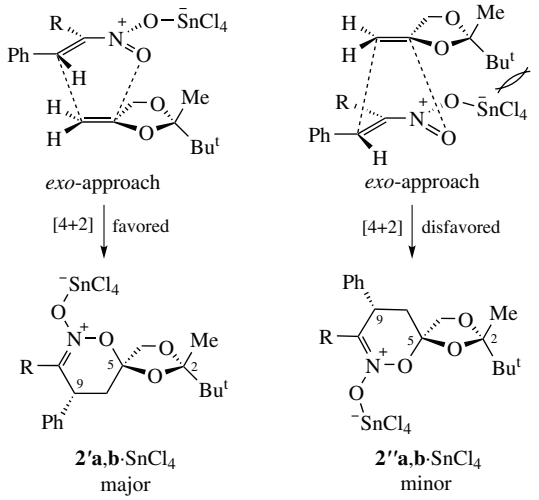
Reaction of compound **1a** with β-nitrostyrene **3a** in the presence of $SnCl_4$ at –78 °C[‡] produced the expected cyclic nitronate **2a** in 53% yield (Scheme 3). Interestingly, only two of four possible diastereomers were formed with the predominance of isomer

† *2-tert-Butyl-2-methyl-4-methylidene-1,3-dioxolane* **1a**. Sodium hydride (2.30 g, 60% suspension in mineral oil, 57.5 mmol) was added to DMSO (30 ml) under dry argon and the mixture was stirred at 70 °C for 1.5 h to give clear solution of dimsyl-Na in DMSO. On cooling to 40 °C, chloride **4a**[8] (9.63 g, 50.0 mmol) was added dropwise for 20 min to the reaction mixture at this temperature to give a brown solution. The mixture was stirred at 40 °C for more 1 h and poured into H_2O (100 ml)/Et_2O (40 ml) mixture. The organic layer was separated and the aqueous one was back-extracted with Et_2O (2×40 ml). Combined organic layers were washed with brine (2×50 ml), dried over Na_2SO_4 and evaporated *in vacuo*. The residue was vacuum distilled over KOH pellets to give 4.37 g (28.0 mmol, 56%) of product **1a** as a colorless liquid, bp 68–70 °C/33 Torr. Being stored at –30 °C over KOH pellets, it would oxidize but can be easily purified by elution through a short pad of Al_2O_3 with hexane. R_f 0.71 (Al_2O_3, hexane, $KMnO_4$ visualization). ^{1}H NMR (400.13 MHz, acetone-d_6, 305 K) δ: 0.98 (s, 9H, CMe_3), 1.31 (s, 3H, Me), 3.79 (q, 1H, =CH_AH$_B$, *J* 1.8 Hz), 4.17 (q, 1H, =CH$_A$$H_B$, *J* 2.0 Hz), 4.48 (dt, 1H, OCH_CH$_D$, *J* 12.3, 1.7 and 1.7 Hz), 4.53 (dt, 1H, OCH$_C$$H_D$, *J* 12.3, 2.0 and 2.0 Hz). ^{13}C NMR (100.61 MHz, acetone-d_6, 305 K) δ: 19.1 (Me), 25.1 (CMe_3), 39.5 (*C*Me$_3$), 67.7 (CH_2), 76.8 (=CH_2), 117.9 (OCO), 158.0 (C=).

‡ *General procedure for the reaction of nitroalkenes* **3** *with* **1a**. $SnCl_4$ (260 μl, 573 mg, 2.2 mmol) was added simultaneously to a stirred solution of nitroalkene **3a**–**c** (2.0 mmol) in CH_2Cl_2 (8 ml) at –78 °C. The reaction mixture was stirred for 15 min and then solution of methylidenedioxolane **1a** (354 mg, 2.2 mmol) in CH_2Cl_2 (2.0 ml) was added dropwise. The reaction mixture was stirred for 2 h at –78 °C and poured into a mixture of EtOAc (20 ml) and saturated aqueous solution of $NaHCO_3$ (15 ml). The aqueous phase was back-extracted with EtOAc (2×10 ml), the combined organic layers were washed with water (20 ml), brine (30 ml) and dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was subjected to column chromatography (silica gel, EtOAc/hexane, 1:3 → 1:2 → 1:1) to give nitronate **2a**,**b** or nitrodiene **5**.



Scheme 3



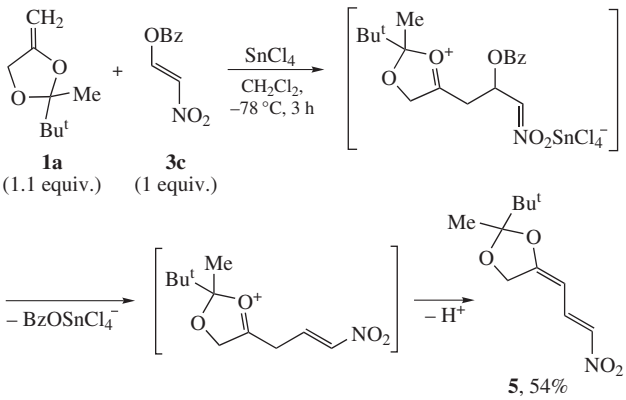
Scheme 4

2′a (ratio **2′a/2″a** = 3.0 : 1.0).[§] Similarly, the reaction of **1a** with β-methyl-β-nitrostyrene **3b** under the same conditions afforded a mixture of diastereomeric nitronates **2′b** and **2″b** with slightly improved diastereoselectivity (*dr* 4.1 : 1.0).[¶]

Analysis of coupling constants along with 2D NOESY spectra data (see Online Supplementary Materials) revealed the 5,9-*trans*-configuration in the 1,2-oxazine ring in both isomers **2′** and **2″**. The isomers differ in the relative configuration of C-2 and C-5 stereocenters in the dioxolane ring. *trans*-Arrangement of *tert*-butyl group and –ON=C fragment was found in the major isomer **2′**, while the minor isomer **2″** had *cis*-configuration of these substituents in dioxolane ring (Scheme 4).

The stereochemical outcome of the [4+2] cycloaddition process is determined by the *exo*/*endo* and diastereofacial selectivities. Both isomers **2′** and **2″** originate from the more sterically favored *exo*-approach[9] of dioxolane **1a** to the nitrostyrene–tin(IV) chloride reactive complex as shown in Scheme 4. The predominance of isomer **2′** results from the addition of nitrostyrene to the less hindered side of dioxolane **1a**, which is opposite to the *tert*-butyl group. Thus, as suggested initially, the remote stereocenter C-2 in dioxolane ring governs the facial selectivity in the [4+2] cycloaddition with nitroalkenes. Evidently, by changing the nature of substituents at C-2 in methylidenedioxolanes **1** the facial stereoselectivity can be further improved.

Unexpectedly, under the same reaction conditions β-benzoyloxy-substituted nitroethylene **3c** did not furnish the corresponding cyclic nitronate. Instead, nitro diene **5** was obtained in 54% yield as a single *E*,*E*-isomer (Scheme 5).[††] The formation of nitro dienes has never been observed in reactions of nitroalkenes with vinyl ethers.[10] The plausible mechanism of nitro diene **5** formation



Scheme 5

[§] *2*-tert-*Butyl-2-methyl-9-phenyl-1,3,6-trioxa-7-azaspiro[4.5]dec-7-ene 7-oxide* **2a**. Yield 324 mg (1.1 mmol, 53%), 3.0 : 1 mixture of diastereomers, white flakes, mp 150–153 °C (Et_2O), R_f 0.49 (SiO_2, EtOAc–hexane, 1:1). ^{1}H NMR (400.13 MHz, $CDCl_3$, 305 K) δ: rel-2*S*,5*S*,9*R*-isomer (major): 1.14 (s, 9H, CMe_3), 1.70 (s, 3H, Me), 2.15 (t, 1H, C$H_{Ax}H_{Eq}$, *J* 12.4 Hz), 2.36 (dd, 1H, CH$_{Ax}H_{Eq}$, *J* 12.8 and 6.7 Hz), 4.03 (d, 1H, OCH_AH_B, *J* 9.5 Hz), 4.15 (ddd, 1H, C*H*Ph, *J* 11.9, 6.7 and 3.1 Hz), 4.35 (d, 1H, OCH$_AH_B$, *J* 9.5 Hz), 6.42 (d, 1H, CH=N, *J* 3.1 Hz), 7.24–7.41 (m, 5H, Ph); rel-2*S*,5*R*,9*S*-isomer (minor): 1.21 (s, 9H, CMe_3), 1.48 (s, 3H, Me), 2.20 (t, 1H, C$H_{Ax}H_{Eq}$, *J* 12.4 Hz), 2.25 (dd, 1H, CH$_{Ax}H_{Eq}$, *J* 12.8 and 7.3 Hz), 4.07 (d, 1H, OCH_AH_B, *J* 9.8 Hz), 4.19 (ddd, 1H, C*H*Ph, *J* 11.2, 7.3 and 3.1 Hz), 4.38 (d, 1H, OCH$_AH_B$, *J* 9.8 Hz), 6.40 (d, 1H, CH=N, *J* 3.1 Hz), 7.24–7.41 (m, 5H, Ph). ^{13}C NMR (100.61 MHz, $CDCl_3$, 305 K) δ: rel-2*S*,5*S*,9*R*-isomer (major): 20.5 (Me), 25.1 (C*Me*$_3$), 34.4 and 38.1 (CH and CH_2), 39.0 (*C*Me$_3$), 74.0 (OCH_2), 108.9 and 119.7 (2OCO), 113.4 (CH=N), 127.4 and 129.2 (*o*-CH_{Ph}, *m*-CH_{Ph}), 128.0 (*p*-CH_{Ph}), 139.2 (*i*-C_{Ph}); rel-2*S*,5*R*,9*S*-isomer (minor): 19.3 (Me), 25.4 (C*Me*$_3$), 35.4 and 37.9 (CH and CH_2), 38.1 (*C*Me$_3$), 73.1 (OCH_2), 107.7 and 119.7 (2OCO), 113.1 (CH=N), 127.5 and 129.1 (*o*-CH_{Ph} and *m*-CH_{Ph}), 127.9 (*p*-CH_{Ph}), 139.3 (*i*-C_{Ph}). HRMS (ESI), *m*/*z*: 328.1518 [M+Na]$^+$ (calc. for $C_{17}H_{23}NNaO_4$, *m*/*z*: 328.1519).

[¶] *2*-tert-*Butyl-2,8-dimethyl-9-phenyl-1,3,6-trioxa-7-azaspiro[4.5]dec-7-ene 7-oxide* **2b**. Yield 295 mg (0.9 mmol, 46%), 4.1 : 1 mixture of diastereomers, white flakes, mp 118–124 °C (Et_2O), R_f 0.53 (SiO_2, EtOAc–hexane, 1:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, 305 K) δ: rel-2*S*,5*S*,9*R*-isomer (major): 1.00 (s, 9H, CMe_3), 1.58 (s, 3H, Me), 1.86 (d, 3H, MeC=N, *J* 1.8 Hz), 2.13 (dd, 1H, C$H_{Ax}H_{Eq}$, *J* 13.2 and 11.4 Hz), 2.27 (dd, 1H, CH$_{Ax}H_{Eq}$, *J* 13.2 and 7.5 Hz), 3.88 (d, 1H, OCH_AH_B, *J* 9.5 Hz), 3.92 (ddd, 1H, C*H*Ph, *J* 11.4, 7.5 and 1.8 Hz), 4.25 (d, 1H, OCH$_AH_B$, *J* 9.5 Hz), 7.13–7.41 (m, 5H, Ph); rel-2*S*,5*R*,9*S*-isomer (minor): 1.07 (s, 9H, CMe_3), 1.34 (s, 3H, Me), 1.85 (d, 3H, MeC=N, *J* 1.5 Hz), 2.14–2.27 (m, 2H, CH$_{Ax}H_{Eq}$), 3.90–4.02 (m, 2H, OCH_AH_B and C*H*Ph), 4.27 (d, 1H, OCH$_AH_B$, *J* 10.0 Hz), 7.13–7.41 (m, 5H, Ph). ^{13}C NMR (100.61 MHz, $CDCl_3$, 305 K) δ: rel-2*S*,5*S*,9*R*-isomer (major): 17.1 (*Me*C=N), 20.5 (Me), 24.9 (C*Me*$_3$), 36.4 (CH_2), 39.0 (*C*Me$_3$), 42.3 (CH), 74.3 (OCH_2), 108.3, 119.6 and 122.2 (2OCO and C=N), 128.4 and 129.8 (*o*-CH_{Ph}, *m*-CH_{Ph} and *p*-CH_{Ph}, overlap), 140.4 (*i*-C_{Ph}); rel-2*S*,5*R*,9*S*-isomer (minor): (selected signals) 17.1 (*Me*C=N), 19.1 (Me), 25.3 (C*Me*$_3$), 37.7 (CH_2), 38.1 (*C*Me$_3$), 42.3 (CH), 73.2 (OCH_2), 107.2 (OCO), 140.6 (*i*-C_{Ph}). HRMS (ESI), *m*/*z*: 320.1856 [M+H]$^+$ (calc. for $C_{18}H_{26}NO_4$, *m*/*z*: 320.1856).

[††] *(*E,E*)-2*-tert-*Butyl-2-methyl-4-(3-nitroprop-2-en-1-ylidene)-1,3-dioxolane* **5**. Yield 245 mg (1.1 mmol, 54%), yellow needles, mp 116–118 °C (Pr^iOH), R_f 0.67 (SiO_2, EtOAc–hexane, 1:1). ^{1}H NMR (300.13 MHz, $CDCl_3$, 298 K) δ: 1.02 (s, 9H, CMe_3), 1.43 (s, 3H, Me), 4.88 (dd, 1H, OCH_AH_B, *J* 14.2 and 1.2 Hz), 4.99 (d, 1H, OCH$_AH_B$, *J* 14.2 and 1.1 Hz), 5.66 (dt, 1H, =CH, *J* 13.2, 1.2 and 1.2 Hz), 7.02 (d, 1H, =CHNO$_2$, *J* 12.8 Hz), 7.53 (t, 1H, =CH, *J* 12.8 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$, 299 K) δ: 19.1 (Me), 24.7 (C*Me*$_3$), 39.0 (*C*Me$_3$), 67.6 (OCH_2), 91.0 (=CH), 121.9 (OCO), 133.3 and 136.6 (2=CH), 166.3 (C=). HRMS (ESI), *m*/*z*: 250.1046 [M+Na]$^+$ (calc. for $C_{11}H_{17}NNaO_4$, *m*/*z*: 250.1050).

involves tin chloride-promoted Michael addition of dioxolane **1a** to nitroalkene **3c** followed by elimination of benzoic acid.

In conclusion, a method for the stereoselective synthesis of previously unavailable spirocyclic nitronates of type **2** by the inverse electron demand [4+2] cycloaddition of nitrostyrenes with methylidenedioxolane **1a** has been developed. The resulting nitronates **2** were obtained with exceptional *exo*-selectivity and reasonable facial selectivity. Structural factors governing the direction of the interaction between methylidenedioxolanes and nitroalkenes were identified. Reaction of methylidenedioxolane **1a** with 2-nitrovinyl benzoate **3c** follows a Michael addition/elimination pathway leading to nitro diene **5** instead of expected cyclic nitronate.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.11.017.

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