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1,3-Dipolar cycloaddition of nitrile oxides to 1-phenylsulfonyl-1,3-butadienes: synthesis of 3-(4,5-dihydroisoxazol-5-yl)pyrroles

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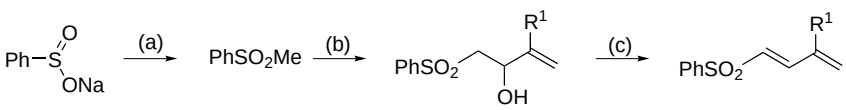
Abstract—Novel heterocyclic compounds containing the 3-(4,5-dihydroisoxazol-5-yl)pyrrole ring system were synthesized in good yields (66–78%) by regioselective 1,3-dipolar cycloaddition of nitrile oxides to 1-phenylsulfonyl-1,3-dienes followed by Barton–Zard pyrrole annulation.

Although 1,3-dipolar cycloaddition of nitrile oxides to alkenes has been extensively studied,[1] examples of their reactions with dienes are rare.[2] 4,5-Dihydroisoxazoles and pyrroles constitute important structural moieties, which occur frequently in natural products and other biologically active compounds.[3] Indeed, interesting routes to diisoxazolines[4] and dipyrroles[5] have been recently reported. Building on this work, we report a convenient synthesis of 3-(4,5-dihydroisoxazol-5-yl)pyrrole-2-carboxylates by a process consisting of the regioselective 1,3-dipolar cycloaddition of nitrile oxides to 1-phenylsulfonyl-1,3-dienes followed by pyrrole annulation using the method pioneered by Schöllkopf[6] and employed more recently by Magnus.[5] To our knowledge, these 3-(4,5-dihydroisoxazol-5-yl)pyrrole products have not been previously reported.

1-Phenylsulfonyl-1,3-butadienes (i.e. **4**) have been successfully employed in a variety of reactions,[7] but there are no reports of their use as dipolarophiles in 1,3-dipolar cycloadditions. The 1-phenylsulfonyl-1,3-butadienes[8] used to explore this novel transformation were synthesized from commercially available benzene-sulfinate sodium salt **1** as follows. Methylation of benzenesulfinate with iodomethane in THF furnished methyl phenyl sulfone **2**[9] in 90% yield. Subsequent 1,2-addition of phenylsulfonylmethyllithium, generated in situ from methyl phenyl sulfone and *n*-BuLi in THF at −78°C, to α,β-unsaturated aldehydes gave 1-phenylsulfonyl-3-alken-2-ols **3** in 95% yield.[10] The target 1-phenylsulfonyl-1,3-butadienes (**4**) were then obtained in excellent yield (**4a**/95% and **4b**/91%; Scheme 1) by acetylation followed by in situ elimination in the presence of DBU.

1-Sulfonyl-1,3-butadiene substrates **4** and **6** were synthesized to evaluate the influence of diene substitution on nitrile oxide (generated from the corresponding oximes with an excess of commercially available bleach) 1,3-dipolar regioselectivity. With diene **4** ($R^1 = H$ or Me), these cycloadditions occur exclusively at the terminal double bond to give **5**[11] as a single isomer (Scheme



1 **2** **3** **4**

90%

a : 95% ; R^1 = H
b : 95% ; R^1 = Me

a : 95%; R^1 = H
b : 91%; R^1 = Me

Scheme 1. *Reagents and conditions*: (a) MeI (5 equiv.), THF, reflux, 12 h; (b) (i) *n*-BuLi (1.1 equiv.), THF, −78°C, 1 h, (ii) CH_2=C(R^1)CHO (1.1 equiv.), −78°C to rt, 30 min, (c) Ac_2O (3 equiv.), DBU (4 equiv.), rt, 1 day.

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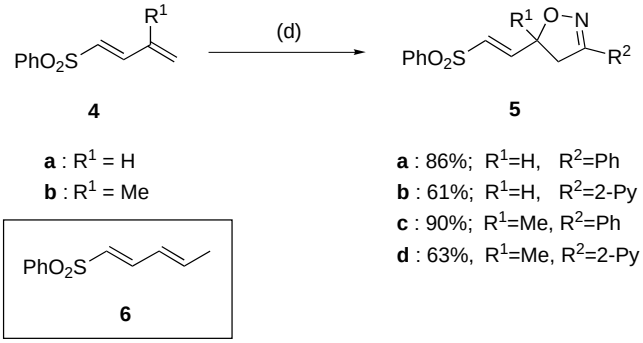


Scheme 2. *Reagents and conditions*: (d) R^2-CH=NOH (1.1 equiv.), aq. NaOCl (2.5 equiv.), CH_2Cl_2, 0°C.

2)[12]—presumably due to the consequence of differing steric hindrances at the two competing C,C-double bonds. We note that both electron rich (R^2 = Ph) and electron poor (R^2 = 2-Py) nitrile oxides perform equally well in this transformation. Not surprisingly, diene **6**, which has only internal C,C-double bonds, fails to react with nitrile oxides under these conditions.

It has been reported that pyrroles are readily prepared from ethyl isocyanoacetate and electron-deficient alkenes, e.g. nitroalkenes[13] and sulfonylalkenes,[14] using a Barton–Zard type reaction[13] in which these electron-deficient alkenes act as Michael acceptors. Since cycloadduct **5** incorporates an electron-deficient sulfonylalkene moiety, it appeared ideally suited for this pyrrole-forming reaction. We set out to construct our 3-(4,5-dihydroisoxazol-5-yl)pyrrole targets using this transformation (Scheme 3).

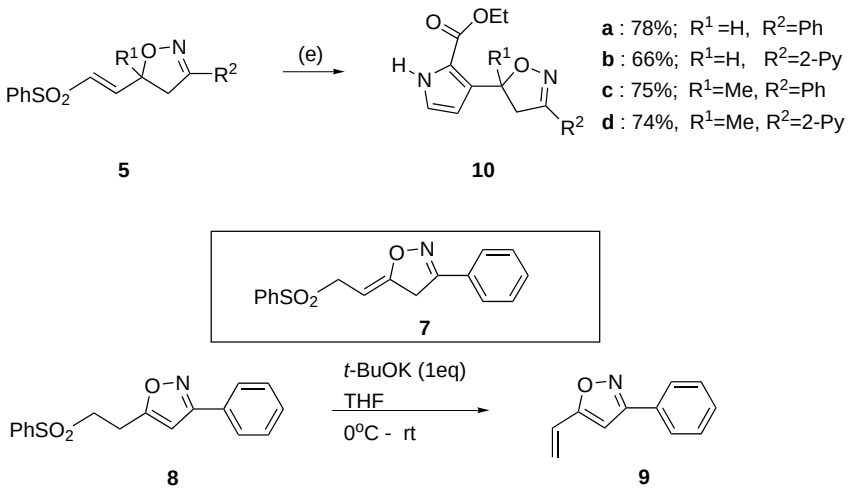
Unfortunately, pyrrole annulation of **5a** with ethyl isocyanoacetate using DBU as base failed to produce the desired pyrrole product. Instead, isoxazole-containing compounds **8**[15] and **9**[16] were obtained suggesting that C,C-double bond isomerization in **5** occurred prior to Michael addition of the ethyl isocyanoacetate enolate. Thus, formation of presumed intermediate **7** followed by aromatization to isoxazole **8** and subsequent sulfinate elimination produced vinyl isoxazole **9**. Indeed, vinyl isoxazole **9** was independently obtained by treating isolated **8** with potassium *t*-butoxide (Scheme 3). Fortunately, treatment of cycloadduct **5a** with the sodium hydride-derived enolate of ethyl isocyanoacetate (EtO_2CCH_2NC/NaH/HMDS/Me_2SO/THF/25°C)[5b,5c,6] gave the desired pyrrole-containing product **10a** in 78% yield (Scheme 3). This modified protocol delivered **10a–d**[17] from **5a** and **5b**.

In summary, the regioselective 1,3-dipolar cycloaddition of nitrile oxides to 1-phenylsulfonyl-1,3-butadienes, which are further transformed to new 3-(4,5-dihydroisoxazol-5-yl)pyrrole heterocycles, has been achieved. The initial 1,3-dipolar cycloaddition is mediated by differential steric hindrance in the two C,C-double bonds of the diene.

Experimental

General procedure for the preparation of compounds 5a: As a typical example, the preparation of **5a** is described. To a solution of benzaldehyde oxime (0.13 g, 1.1 mmol) in CH_2Cl_2 (8 mL) was added 0.5 M 1-phenylsulfonyl-1,3-diene solution in CH_2Cl_2 (2 mL, 1 mmol),[18] and the solution was cooled to 0°C. Aqueous NaOCl (5.25%; 3.5 g, 2.5 mmol) was added dropwise over 30 min, and the reaction was stirred overnight (0°C→room temperature) at which time the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by recrystallization from CH_2Cl_2/Et_2O to give **5a** (0.27 g, 86%). Isoxazolines **5b–d** were also prepared in 61, 90, and 63% yields, respectively, under similar reaction conditions.

General procedure for the preparation of compounds 10a: As a typical example, the preparation of **10a** is described. To a solution of 5-((*E*)-2-benzenesulfonylvinyl)-3-phenyl-4,5-dihydroisoxazole **5a** (0.31 g,



Scheme 3. *Reagents and conditions*: (e) $CNCH_2CO_2Et$ (1.2 equiv.), NaH (1.35 equiv.), HMDS (1.35 equiv.), DMSO (8.3 equiv.), THF, 0°C to rt.

1.0 mmol) and ethyl isocyanoacetate (0.13 mL, 1.2 mmol) in THF (6 mL) was added dropwise a solution of 60% sodium hydride (0.054 g, 1.35 mmol) and 1,1,1,3,3,3-hexamethyldisilazane in THF (4 mL) at 0°C. DMSO (0.59 mL) was added to this reaction mixture, which was stirred overnight (0°C→room temperature). The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3×30 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), and evaporated in vacuo. Column chromatography of the residue over silica gel eluting with *n*-hexane/EtOAc (4:1) gave **10a** (0.22 g, 78%). Other products (**10b–d**) were also prepared in 66, 75, and 74% yields, respectively, under similar reaction conditions.

Acknowledgements

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10. (a) Wada, E.; Pei, W.; Yasuoka, H.; Chin, U.; Kanemasa, S. *Tetrahedron* **1996**, *52*, 1205–1220; (b) Compound **3b**: White solid (CH_2Cl_2/*n*-hexane); mp 77°C; IR (neat) 3450, 1283, 1134 cm^{-1}; ^1H NMR δ 7.98–7.94 (m, 2H), 7.72–7.57 (m, 3H), 5.04 (d, $J=0.9$ Hz, 1H), 4.90 (m, 1H), 4.60 (d, $J=9$ Hz, 1H), 3.32 (dd, $J=14$ and 9 Hz, 1H), 3.27 (br s, 1H), 3.24 (dd, $J=14$ and 2.5 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR δ 143.61, 139.22, 134.14, 129.49, 128.06, 113.11, 69.80, 61.30, 18.09. Anal. calcd for $C_{11}H_{14}O_3S$: C, 58.38; H, 6.24; S, 14.17. Found: C, 58.49; H, 6.26; S, 13.96.
11. (a) **5-((*E*)-2-Benzenesulfonylvinyl)-3-phenyl-4,5-dihydroisoxazole (5a)**: White solid (CH_2Cl_2/Et_2O); mp 180°C; IR (neat) 1303.0, 1142.8 cm^{-1}; ^1H NMR δ 7.90–7.87 (m, 2H), 7.64–7.61 (m, 3H), 7.57–7.52 (m, 2H), 7.44–7.40 (m, 3H), 6.98 (dd, $J=15.0$ and 4.7 Hz, 1H), 6.72 (dd, $J=15.0$ and 1.4 Hz, 1H), 5.40–5.32 (m, 1H), 3.65 (dd, $J=16.6$ and 11.3 Hz, 1H), 3.23 (dd, $J=16.6$ and 7.1 Hz, 1H); ^{13}C NMR δ 156.03, 142.04, 139.67, 133.78, 132.10, 130.68, 129.46, 128.90, 128.59, 127.89, 126.86, 78.01, 40.73. Anal. calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47; S, 10.23. Found: C, 65.05; H, 4.87; N, 4.47; S, 10.43; (b) **2-[5-((*E*)-2-Benzenesulfonylvinyl)-4,5-dihydroisoxazol-3-yl]pyridine (5b)**: Separated and purified by recrystallization using CH_2Cl_2/Et_2O. White solid; mp 194.5°C; IR (neat) 1302, 1280, 1144 cm^{-1}; ^1H NMR δ 8.61–8.59 (m, 1H), 7.98 (dt, $J=8$ and 1 Hz, 1H), 7.91–7.87 (m, 2H), 7.73 (dt, $J=8$ and 1.8 Hz, 1H), 7.67–7.61 (m, 1H), 7.60–7.52 (m, 2H), 7.32 (ddd, $J=7.5$, 4.9 and 1.2 Hz, 1H), 6.99 (dd, $J=15$ and 4.5 Hz, 1H), 6.71 (dd, $J=15$ and 1.6 Hz, 1H), 5.44–5.35 (m, 1H), 3.75 (dd, $J=17.6$ and 11.5 Hz, 1H), 3.41 (dd, $J=17.6$ and 7.2 Hz, 1H); ^{13}C NMR δ 158.00, 149.43, 148.43, 142.10, 139.67, 136.54, 133.75, 131.90, 129.44, 127.90, 124.74, 121.92, 78.63, 40.41. Anal. calcd for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91; S, 10.20. Found: C, 60.90; H, 4.56; N, 8.71; S, 10.08; (c) **5-((*E*)-2-Benzenesulfonylvinyl)-5-methyl-3-phenyl-4,5-dihydroisoxazole (5c)**: Separated and purified by recrystallization using CH_2Cl_2/Et_2O. White solid; mp 158°C; IR (neat) 1314, 1306, 1143 cm^{-1}; ^1H NMR δ 7.89–7.86 (m, 2H), 7.63–7.51 (m, 5H), 7.42–7.37 (m, 3H), 7.03 (d, $J=14.8$ Hz, 1H), 6.70 (d, $J=14.8$ Hz, 1H), 6.64 (dd, $J=25.0$ and 16.8 Hz, 2H), 1.62 (s, 3H); ^{13}C NMR δ 156.03, 145.86, 139.76, 133.70, 130.50, 130.21, 129.42, 128.98, 128.83, 127.79, 126.64, 85.00, 46.47, 25.42. Anal. calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28; S, 9.79. Found: C, 65.97; H, 5.30; N, 4.16; S, 9.69; (d) **2-[5-((*E*)-2-Benzenesulfonylvinyl)-5-methyl-4,5-dihydroisoxazol-3-yl]-pyridine (5d)**: Separated and purified by recrystallization using CH_2Cl_2/Et_2O. White solid; mp 149.2°C; IR (neat) 1304, 1146 cm^{-1}; ^1H NMR δ 8.59–8.56 (m, 1H), 7.97–7.94 (m, 1H), 7.89–7.86 (m, 2H), 7.72 (dt, $J=8$ and 1.8 Hz, 1H), 7.65–7.60 (m, 1H), 7.56–7.51 (m, 2H), 7.32–7.25 (m, 1H), 7.04 (d, $J=14.9$ Hz, 1H), 6.67 (d, $J=14.9$ Hz, 1H), 3.47 (dd, $J=28.5$ and 17.6 Hz, 2H), 1.63 (s, 3H); ^{13}C NMR δ 157.98, 149.37, 148.80, 145.92, 139.84, 136.48, 133.67, 130.11, 129.41, 127.83, 124.59, 121.66, 85.78, 46.15, 25.47. Anal. calcd for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 61.87; H, 5.00; N, 8.40; S, 10.01.
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15. Compound **8**: white solid; mp 111.5°C; IR 1308, 1135 cm^{-1}; ^1H NMR δ 7.96–7.93 (m, 2H), 7.74–7.56 (m, 5H), 7.46–7.42 (m, 3H), 6.33 (s, 1H), 3.55–3.50 (m, 2H), 3.30–3.25 (m, 2H); ^{13}C NMR δ 168.58, 162.53, 138.36, 134.18, 130.13, 129.54, 128.94, 128.68, 128.13, 126.74, 100.44, 53.59, 20.99. Anal. calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47; S, 10.23. Found: C, 65.36; H, 4.83; N, 4.44; S, 10.13.

16. (a) Shionogi and Co. Ltd., JP 23172, 1963; (b) *Chem. Abstr*. **1966**, *64*, 15891c. Treatment of compound **5a** with 1 equiv. of sodium hydride gave compound **9** exclusively.
17. (a) **3-(3-Phenyl-4,5-dihydroisoxazol-5-yl)-1*H*-pyrrole-2-carboxylic acid ethyl ester (10a)**: White solid (CH_2Cl_2/Et_2O); mp 87°C; IR (neat) 3295, 1676 cm^{-1}; ^1H NMR δ 9.07 (br s, 1H), 7.72–7.66 (m, 2H), 7.42–7.37 (m, 3H), 6.88 (t, $J=2.75$ Hz, 1H), 6.40 (t, $J=2.75$ Hz, 1H), 6.28 (dd, $J=10.85$ and 7.8 Hz, 1H), 4.36 (q, $J=7.14$ Hz, 2H), 3.81 (dd, $J=16.6$ and 10.85 Hz, 1H), 3.27 (dd, $J=16.6$ and 7.8 Hz, 1H), 1.38 (t, $J=7.14$ Hz, 3H); ^{13}C NMR δ 160.77, 156.36, 132.00, 129.98, 129.73, 128.68, 126.71, 122.21, 118.31, 108.95, 77.13, 60.66, 43.13, 14.70. Anal. calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.78; H, 5.63; N, 9.89; (b) **3-(3-Pyridin-2-yl-4,5-dihydroisoxazol-5-yl)-1*H*-pyrrole-2-carboxylic acid ethyl ester (10b)**: Separated and purified by silica gel column chromatography using *n*-hexane/EtOAc (7:3 v/v). White solid (CH_2Cl_2/Et_2O); mp 122.5°C; IR (neat) 3176, 1684 cm^{-1}; ^1H NMR δ 9.08 (br s, 1H), 8.59 (ddd, $J=4.94$, 1.65, and 1.1 Hz, 1H), 8.06 (dt, $J=8$ and 1.1 Hz, 1H), 7.76–7.70 (m, 1H), 7.31–7.25 (m, 1H), 6.88 (t, $J=2.8$ Hz, 1H), 6.38 (dt, $J=2.8$ and 0.6 Hz, 1H), 6.33 (dd, $J=11$ and 8 Hz, 1H), 4.35 (q, $J=7.1$ Hz, 2H), 3.92 (dd, $J=17.6$ and 11 Hz, 1H), 3.45 (dd, $J=17.6$ and 7.7 Hz, 1H), 1.38 (t, $J=7.14$ Hz, 3H); ^{13}C NMR δ 160.81, 158.21, 149.59, 149.28, 136.38, 131.51, 124.16, 122.09, 121.80, 118.58, 108.94, 77.91, 60.71, 42.64, 14.68. Anal. calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.08; H, 5.41; N, 14.63; (c) **3-(5-Methyl-3-phenyl-4,5-dihydroisoxazol-5-yl)-1*H*-pyrrole-2-carboxylic acid ethyl ester (10c)**: Separated and purified by silica gel column chromatography using *n*-hexane/EtOAc (4:1 v/v). White solid (Et_2O/*n*-hexane); mp 79.8°C; IR (neat) 3321, 1688 cm^{-1}; ^1H NMR δ 9.12 (br s, 1H), 7.68–7.65 (m, 2H), 7.38–7.34 (m, 3H), 6.82 (t, $J=2.7$ Hz, 1H), 6.57 (t, $J=2.7$ Hz, 1H), 4.35 (q, $J=7.1$ Hz, 2H), 3.63 (dd, $J=19.2$ and 17.0 Hz, 2H), 1.85 (s, 3H), 1.39 (t, $J=7.1$ Hz, 3H); ^{13}C NMR δ 159.98, 157.03, 137.73, 130.20, 129.77, 128.60, 126.58, 121.05, 116.53, 110.02, 86.34, 60.53, 48.61, 27.57, 14.73. Anal. calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.33; H, 6.04; N, 9.33; (d) **3-(5-Methyl-3-pyridin-2-yl-4,5-dihydroisoxazol-5-yl)-1*H*-pyrrole-2-carboxylic acid ethyl ester (10d)**: Separated and purified by silica gel column chromatography using *n*-hexane/EtOAc (7:3 v/v). White solid (CH_2Cl_2/Et_2O); mp 143.7°C; IR (neat) 3143, 1693 cm^{-1}; ^1H NMR δ 9.11 (br s, 1H), 8.58–8.56 (m, 1H), 8.0 (d, $J=7.97$ Hz, 1H), 7.69 (dt, $J=8$ and 1.7 Hz, 1H), 7.26–7.22 (m, 1H), 6.82 (t, $J=2.8$ Hz, 1H), 6.55 (t, $J=2.8$ Hz, 1H), 4.38–4.30 (m, 2H), 3.75 (dd, $J=24.4$ and 17.9 Hz, 2H), 1.87 (s, 3H), 1.37 (t, $J=7.15$ Hz, 3H); ^{13}C NMR δ 160.02, 158.77, 149.97, 149.23, 137.04, 136.24, 123.95, 121.57, 120.93, 116.84, 109.81, 87.31, 60.60, 48.40, 27.60, 14.65. Anal. calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.24; H, 5.69; N, 13.94.
18. Since these compounds are easily polymerized in the pure state, a CH_2Cl_2 solution was prepared for use in the reaction. Regarding the polymerization of these compounds, see Ref. 5b.