

New 1,3,4-thiadiazolium-3-(unsubstituted) methanide 1,3-dipoles (azolium 1,3-dipoles): useful synthons at $-60\text{ }^{\circ}\text{C}$: a new ring interconversion route to 1,2,3-trisubstituted and 1,2,3,4-tetrasubstituted 1- $\{[1-(\text{vinylthio})-1\text{-phenylmethylidene}]\text{amino}\}$ pyrroles

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1,3,4-Thiadiazolium-3-(unsubstituted) methanides have been trapped with substituted alkyne dipolarophiles at $-60\text{ }^{\circ}\text{C}$ giving high yields of 2,3-di- and 2,3,4-tri-substituted 1- $\{[1-(\text{vinylthio})-1\text{-phenylmethylidene}]\text{amino}\}$ pyrroles from a cycloaddition rearrangement sequence. The conformation of these molecules results in an unusual proton shielding effect in the ^1H NMR spectra. An X-ray crystal structure is reported for methyl 1- $\{(Z)\text{-}1\text{-}\{(Z)\text{-}2\text{-methoxycarbonylvinylthio}\}\text{-}1\text{-phenylmethylideneamino}\}\text{-}2\text{-phenyl-}1H\text{-pyrrole-}3\text{-carboxylate}$ **7a**.

Our interest in exploring the synthetic potential of the exocyclic ylides of higher azolium systems as 1,3-dipoles¹ led to a recent² attempt to generate the furazan-*N*-methanide analogue of the furoxan system. However the 1,2,5-oxadiazolium-2-methanide, if it existed at all, was too fleeting to be useful in cycloaddition–rearrangement sequences and it could not be trapped. Herein we have generated, and trapped, the 1,3,4-thiadiazolium-3-methanide species **2**. At ambient temperatures, and even down to $-30\text{ }^{\circ}\text{C}$ these new species are unstable and they decompose to intractable resins. However at $-60\text{ }^{\circ}\text{C}$ they exhibit clean high-yield cycloaddition–rearrangement reactions. These provide a new synthesis of 1,2,3-trisubstituted pyrroles as well as a route to 1,2,3,4-tetrasubstituted pyrrole derivatives. Despite the range of known routes to the pyrrole ring system the 1,2,3-trisubstituted pattern is particularly difficult to achieve because electrophilic substitution occurs predominantly at the 2-position.³ There is still a need to develop new routes to specially substituted pyrroles because of their great importance as intermediates in the synthesis of natural products.^{3,4}

Results and discussion

The salts **1** were prepared by treating the parent 1,3,4-thiadiazoles⁵ with trimethylsilylmethyl trifluoromethanesulfonate in dry dichloromethane at $50\text{ }^{\circ}\text{C}$. The dipoles **2** were generated from these by a literature desilylation procedure^{6,7} using CsF at $-60\text{ }^{\circ}\text{C}$ in the presence of an excess of the substituted alkyne which trapped the dipole. The reactions between the dipole **2** and dialkyl acetylenedicarboxylates gave the products **5** and **6** (Table 1). With methyl propiolate as dipolarophile the reaction was regioselective and gave the products **7**. We view

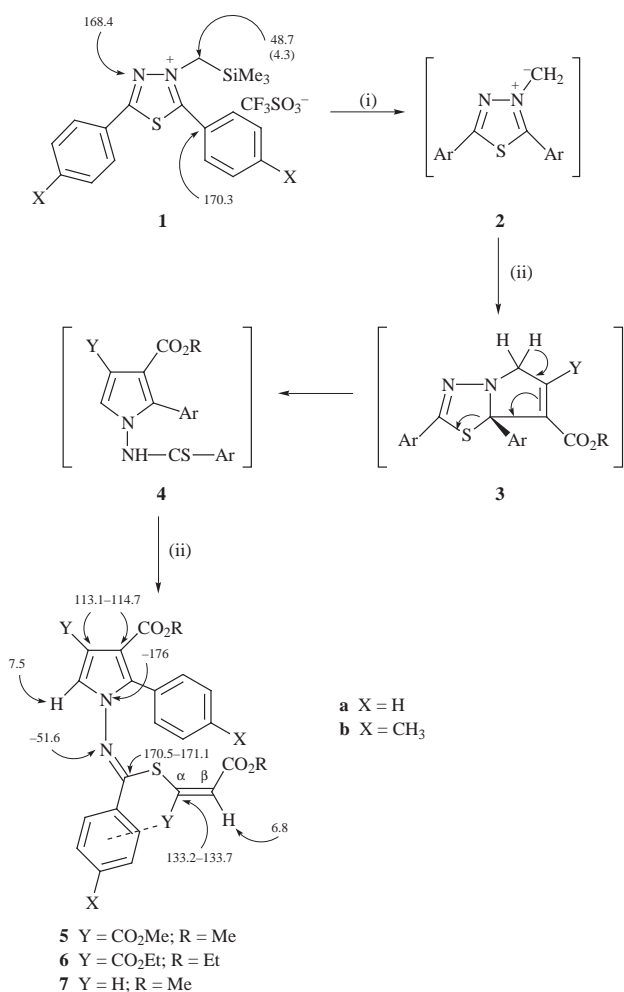
the reaction as a 1,3-dipolar cycloaddition, the first such case with exocyclic 1,3,4-thiadiazolium ylide systems, followed by an aromatisation of cycloadducts **3** via a 1,4-conjugate elimination⁸ process giving rise to the 1-(thioamido)pyrroles **4**. In the presence of an excess of alkyne these undergo a Michael type reaction giving the products **5**, **6** and **7** from S–H addition with the thioamide. The same products were obtained as the reaction temperature was raised to $-40\text{ }^{\circ}\text{C}$ but the yields declined sharply due to decomposition of the dipoles.

The structures of the products were established from microanalyses, IR, ^1H and ^{13}C NMR spectroscopy, including DEPT and off-resonance decoupled spectroscopy, which showed all of the expected signals (Scheme 1, Experimental). The ^{15}N NMR spectrum of compound **7a** showed the pyrrole N atom at -176.0 ppm and the imino N atom at -51.6 ppm in agreement with literature⁹ values for such structures thereby confirming the addition of the second alkyne molecule at the S atom rather than the N atom of the thioamido function of **4**. NOE effects were observed between the Y group and the pyrrole 2-CH and 5-aryl groups as well as with the *cis*-vicinal olefinic H atom ($J_{\alpha,\beta}$ 10.1 Hz), thereby confirming the alkene *E*-configuration. In the ^1H NMR spectra of **5**, **6** and **7** exceptional shielding was exhibited by the Y group at the vinylic α -site (see Scheme 1 for α -position). Thus for compound **5a** the MeO group at this site was shielded to 3.3 ppm while the remaining three MeO groups appeared at normal values of 3.76–3.83 ppm. In compound **7a** this specially shielded MeO was absent but the vinylic α -H atom which replaced it showed exceptional shielding, appearing at 5.8 ppm and being more upfield than the β -vinylic H atom (6.55 ppm) which is unusual for a vinylic system.¹⁰ An X-ray crystal structure of compound **7a** (Fig. 1) confirmed the structural assignments including the regioselectivity and

Table 1 Formation of products **5**, **6** and **7**

Entry	Compound (Substrate)	Mp ($T^{\circ}\text{C}$)	Yield (%)	Compound (Product)	Mp/ $^{\circ}\text{C}$	Yield (%)
1	1a	128	100	5a	131	80 ^a (36)
2	1b ^c	148–150	100	5b	144–145	74 ^a
3	1a	128	100	6a	oil	73 ^a
4	1b ^c	148–150	100	6b	114–116	76 ^a
5	1a	128	100	7a	121–122	93 ^b
6	1b ^c	148–150	100	7b	oil	85 ^b

^a Reactions at $-60\text{ }^{\circ}\text{C}$ in CH_2Cl_2 using 6 mol. equiv. of alkyne; where shown, parentheses contain yields with 2 mol. equiv. of alkyne. ^b Using 35 mol. equiv. of alkyne; all products were recrystallized from CHCl_3 –hexane. ^c Substrate **1b** prepared and purified as described for **1a**.



Scheme 1 Some ¹H, ¹³C and ¹⁵N NMR shift ranges shown for **1**, **5** and **6**. Reagents and conditions: (i) CsF in CH₂Cl₂, -60 °C; (ii) alkyne dipolarophiles, dimethyl and diethyl acetylenedicarboxylate and methyl propiolate

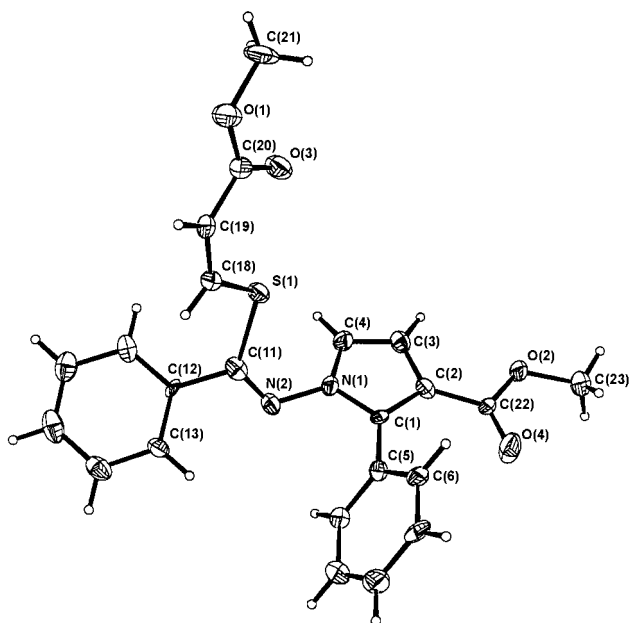


Fig. 1 X-Ray crystal structure of compound **7a**

explained the exceptional shielding of the vinylic α -site in these new pyrrole derivatives. The calculated position for the vinylic α -H atom is over the nearby phenyl ring and is 3.27 Å from the ring centroid and therefore experiences the intense shielding of this region. It may also be picking up shielding from the pyrrole

ring current since this ring is similarly aligned relative to the Y group.

Experimental

Mps were measured on an Electrothermal apparatus. The 2,5-diaryl-1,3,4-thiadiazoles were prepared by literature procedures.⁵ Low temperature reactions employed a Wheaton jacketed flask with the ports connected to a cold methanol bath. NMR spectra were measured on a JEOL GXFT 400 NMR machine and IR spectra on a Perkin-Elmer 983G spectrophotometer. The following examples show typical experimental procedures.

2,5-Diphenyl-3-trimethylsilylmethyl-1,3,4-thiadiazolium triflate **1a**

A solution of 2,5-diphenyl-1,3,4-thiadiazole⁵ (1.07 g, 4.5 mmol) and trimethylsilylmethyl trifluoromethanesulfonate (1.8 cm³, 9.0 mmol) in dry CH₂Cl₂ (5 cm³) was stirred at 50 °C under a reflux condenser for 24 h, evaporated under reduced pressure and the white residue washed with diethyl ether to give 2,5-diphenyl-3-trimethylsilylmethyl-1,3,4-thiadiazolium triflate **1a**, mp 128 °C (from CH₂Cl₂-Et₂O) (100%) (Found: C, 48.0; H, 4.1; N, 5.7. C₁₉H₂₁F₃N₂O₃S₂Si requires C, 48.0; H, 4.4; N, 5.9%); δ_{H} (CDCl₃) 0.16 (s, 9H, SiMe₃), 4.3 (s, 2H, CH₂-N), 7.5–7.8 (m, 6H, Ph, H_{meta,para}), 7.92–7.98 (m, 4H, Ph, H_{ortho}); δ_{C} -2.3 (SiMe₃), 48.7 (N-CH₂), 168.4 (C-5), 170.3 (C-2), 121.9, 134.0, 129.9, 126.0 (2-C-Ph, C-1', C-2', C-3', C-4' resp.), 126.0, 133.8, 129.7, 127.8 (5-C-Ph, C-1', C-2', C-3', C-4' resp.).

Dimethyl 1-[(Z)-1-[(Z)-1,2-dimethoxycarbonylvinyllthio]-1-phenylmethylideneamino]-2-phenyl-1H-pyrrole-3,4-dicarboxylate **5a** (Table 1, entry 1)

A solution of the salt **1a** (0.49 g, 1.02 mmol) and dimethyl acetylenedicarboxylate (DMAD) (0.75 cm³, 6.12 mmol) in CH₂Cl₂ (10 cm³) was cooled to -60 °C, treated with CsF (300 mg, 2 mmol), stirred for 5 days, warmed to ambient temperature and filtered to remove the salts. After evaporation under reduced pressure the residue was dissolved in dichloromethane (2 cm³) and placed on a silica gel-60 column (70–230 mesh ASTM). Elution with a mixture of diethyl ether-ethyl acetate-hexane (1:1:4 by volume) gave **5a**, mp 131 °C (from CHCl₃-hexane) (0.44 g, 80%) (Found: C, 60.4; H, 4.5; N, 5.3. C₂₇H₂₄N₂O₈S requires C, 60.4; H, 4.5; N, 5.2%); ν_{max} (mull)/cm⁻¹ 1725.1, 1701.6 (ester C=O), 1607 (C=N), 1572 (C=C vinylic), 3060.3 (C-H vinylic); δ_{H} (CDCl₃) 3.3 (shielded OMe), 3.76, 3.82, 3.83 (s, 3H each, OMe), 6.8 (s, 1H, vinylic β -H), 7.3–7.6 (m, 10H, Ph), 7.54 (s, 5-CH); δ_{C} 51.4, 51.9, 52.4, 53.2 (each OMe), 162.9, 163.6, 164.2, 165.7 (each C=O), 171.1 (C=N), 113.2, 114.3 (pyrrole C-3, C-4), 134.3 (C-2), 131.8 (5-CH), 139.2 (vinyl α -C), 121.8 (vinyl β -CH), 133.2, 129.9, 128.5, 129.1 (2-C-Ph, C-1', C-2', C-3', C-4' resp.), 128.9, 129.3, 127.8, 128.3 (iminyl, Ph, C-1', C-2', C-3', C-4' resp.); δ_{N} (in CDCl₃ from CH₃NO₂) -56.9 (iminyl nitrogen), -177.7 (pyrrole nitrogen).

Diethyl 1-[(Z)-1-[(Z)-1,2-diethoxycarbonylvinyllthio]-1-(4-methylphenyl)methylideneamino]-2-(4-methylphenyl)-1H-pyrrole-3,4-dicarboxylate **6b** (Table 1, entry 4)

A solution of the salt **1b** (0.51 g, 1.02 mmol) and diethyl acetylenedicarboxylate (DEAD) (0.98 cm³, 6.12 mmol) in CH₂Cl₂ (10 cm³) cooled at -60 °C was treated as previously described. The column was eluted with a mixture of pentane-ethyl acetate (4:1 by volume) to give **6b**, mp 114–116 °C (from CHCl₃-hexane) (76%) (Found: C, 63.9; H, 6.0; N, 4.4. C₃₃H₃₆N₂O₈S requires C, 63.9; H, 5.9; N, 4.5%); ν_{max} (mull)/cm⁻¹ 1716.6, 1695.7 (ester C=O), 1601.7 (C=N), 1572.1 (C=C vinylic), 3072.0 (C-H vinylic); δ_{H} (CDCl₃) 1.02 (t, 3H, *J* 7.1, shielded OCH₂CH₃), 1.20–1.36 (3 overlapping triplets, 9H, OCH₂CH₃), 2.33 (s, 3H, 4-Me), 2.34 (s, 3H, 4-Me), 3.82 (q, 2H, shielded OCH₂CH₃), 4.2–4.3 (3 overlapping quartets, 6H, OCH₂CH₃), 6.8 (s, 1H, vinylic H), 7.14–7.16 (m, 4H, Ar), 7.41–7.45 (m, 4H,

Table 2 Crystal data and structural refinement for **7a**

Empirical formula	C ₂₃ H ₂₀ N ₂ O ₄ S
Formula weight (amu)	420.47
<i>T</i> /K	293(2)
$\lambda/\text{\AA}$	0.710 69
Crystal system	monoclinic
Space group	<i>P</i> 2 ₁ / <i>n</i>
Unit cell dimensions	<i>a</i> = 9.119(3) \AA, <i>b</i> = 26.092(5) \AA, β = 112.93(2)° <i>c</i> = 9.646(3) \AA
<i>V</i> /\AA ³	2113.6(10)
<i>Z</i>	4
<i>D_c</i> /Mg m ⁻³	1.321
μ/mm^{-1}	0.185
<i>F</i> (000)	880
Crystal size/mm	0.45 × 0.32 × 0.15
θ range for data collection/°	2.42–20.81
Index ranges	−9 ≤ <i>h</i> ≤ 8; −3 ≤ <i>k</i> ≤ 26; 0 ≤ <i>l</i> ≤ 9
Reflections collected	2496
Independent reflections	2214 [<i>R</i> (int) = 0.0914]
Reflections observed (>2 σ)	1657
Refinement method	Full-matrix least-squares on <i>F</i> ²
Data/restraints/parameters	2214/0/273
Goodness-of-fit on <i>F</i> ²	1.002
Final <i>R</i> indices [<i>I</i> > 2 σ (<i>I</i>)]	<i>R</i> ₁ = 0.0594, ωR ₂ = 0.1516
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0778, ωR ₂ = 0.1622
Largest diff. peak and hole/e \AA ⁻³	0.373 and −0.471

R indices; $R_1 = \sum ||F_o| - F_c| / \sum |F_o|$ (based on *F*), $\omega R_2 = \{[\sum_w (F_o^2 - F_c^2)^2] / [\sum_w (F_o^2)^2]\}^{1/2}$ (based on *F*²). $\omega = 1 / \{(\sigma F_o)^2 + (0.1313 * P)^2\}$
 Goodness-of-fit = $[\sum_w (F_o^2 - F_c^2)^2 / (\text{Nobs} - \text{Nparameters})]^{1/2}$.

Ar), 7.57 (s, 5-CH); δ_C 14.4, 14.2, 14.0, 13.7 (each OCH₂CH₃), 21.4, 21.5 (each 4-Me), 60.2, 60.9, 61.7, 63.0 (each OCH₂CH₃), 162.8, 163.6, 164.2, 165.6 (each C=O), 170.5 (C=N), 113.6, 114.4 (pyrrole C-3, C-4), 133.7 (C-2), 132.0 (5-CH), 140.1 (vinyl α -C), 121.6 (vinyl β -CH), 128.9, 130.1, 129.3, 142.6 (2-C-Ph, C-1', C-2', C-3', C-4' resp.), 126.3, 129.71, 128.6, 138.1 (iminyl, Ph, C-1', C-2', C-3', C-4' resp.).

Methyl 1-[(*Z*)-1-[(*Z*)-2-methoxycarbonylvinylothio]-1-phenyl-methylideneamino]-2-phenyl-1*H*-pyrrole-3-carboxylate **7a (Table 1, entry 5)**

A solution of the salt **1a** (0.49 g, 1.012 mmol) and methyl propiolate (3.18 cm³, 35.7 mmol) in CH₂Cl₂ was cooled to −60 °C and treated as described. The column was eluted with CH₂Cl₂ to give the product **7a**, mp 121–122 °C (from CHCl₃–hexane) (93%) (Found: C, 65.6; H, 4.8; N, 6.5. C₂₃H₂₀N₂O₄S requires C, 65.6; H, 4.8; N, 6.6%); ν_{max} (mull)/cm⁻¹ 1716.0, 1702.4 (ester C=O), 1599.6 (C=N), 1576.2 (C=C vinylic), 3060.3 (C-H vinylic); δ_H (CDCl₃) 3.70, 3.73 (s, each 3H, OMe), 5.8 [d, 1H, α -vinylic H (shielded), *J* 10.1], 6.55 (d, 1H, *J* 10.1, β -vinylic H), 6.79 (d, 1H, 4-CH, *J* 2.9), 6.83 (d, 1H, 5-CH, *J* 2.9), 7.3–7.5 (m, 10H, 2 Ph); δ_C 50.5, 51.5 (each OMe), 164.5, 165.7 (each C=O), 172.9 (C=N), 109.7 (pyrrole C-4), 111.4 (pyrrole C-3), 134.1 (C-2), 131.5 (5-CH), 139.8 (vinyl α -CH), 115.8 (vinyl β -CH), 133.3, 130.8, 128.7, 117.1 (2-C-Ph, C-1', C-2', C-3', C-4' resp.), 129.8,

129.2, 127.1, 127.9 (iminyl, Ph, C-1', C-2', C-3', C-4' resp.); δ_N (in CDCl₃ from CH₃NO₂) −51.6 (iminyl nitrogen), −176.0 (pyrrole nitrogen).

X-Ray crystallography

Crystal data for compound **7a** are given in Table 2. The structure was solved by direct methods, SHELXS-97,¹¹ and refined by full-matrix least-square using SHELX-97.¹² SHELX operations were rendered paperless using ORTEP which was also used to obtain the drawings.¹³ Data were corrected for Lorentz and polarization effects but not for absorption. Hydrogen atoms were included in calculated positions with thermal parameters 30% larger than the atom to which they were attached. The non-hydrogen atoms were refined anisotropically. All calculations were performed on a Pentium PC.

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available via the RSC Web page (<http://www.rsc.org/authors>). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/192.

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