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Synthesis of 2-iminothiazoline derivatives by sequential conjugate addition/annulation/ring-opening reactions

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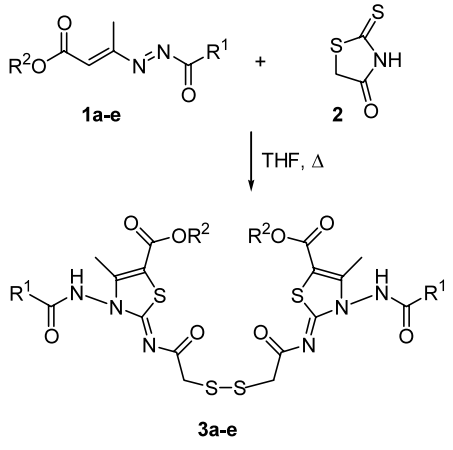
Abstract—1,2-Diaza-1,3-butadienes reacted with rhodanine affording 2-(mercaptoacetyl)iminothiazoline derivatives through conjugate addition/annulation/ring-opening/oxidative dimerization. The hypothesized ring-closure and ring-opening mechanism was supported by X-ray crystal structure analysis of a compound obtained by reaction of the same reagents with a chiral 1,3-oxazolidine-2-thione derivative.

The electronic features of 1,2-diaza-1,3-butadienes[1] favor regioselective nucleophilic attack at C-4 by a variety of carbon- and hetero-nucleophiles[2] defining their use as versatile building blocks for the construction of heterocyclic rings. Since the resulting Michael adducts bear suitable nucleophilic and electrophilic centres, a cyclization reaction can follow the addition step. This process represents a valuable method to afford pyrroles, pyrazoles, imidazoles, pyridazines, thiazolinones, thiazoles, selenazoles and thiadiazoles.[3]

With our ongoing effort aimed at developing synthetic strategies to prepare polyfunctionalised thiazole derivatives,[4] we explored the reactivity of 1,2-diaza-1,3-butadienes **1** with rhodanine **2** as a route to 4-thiazolidinone derivatives. One of the main targets of our studies is the reaction of 1,2-diaza-1,3-butadienes with *S*-nucleophiles. Thiazolidinone derivatives of rhodanine are reported to have antibacterial, antiviral, pesticidal, anti-inflammatory and anti-diabetic properties.[5] Recently, synthesis of an arylalkylidene rhodanine library and the modification of the rhodanine side chain resulted in increased selectivity towards hepatitis C virus (HCV) NS3 protease.[6] In addition, a novel series of bis-thiazole derivatives showed promising anticancer activity against human cell lines.[7] Hence, a new synthetic method to prepare such thiazolidinones would represent a useful application in medicinal chemistry.



Scheme 1. Reaction between 1,2-diaza-1,3-butadienes **1a–e** and rhodanine.

Keywords: conjugate addition; annulation; ring-opening; dimerization.

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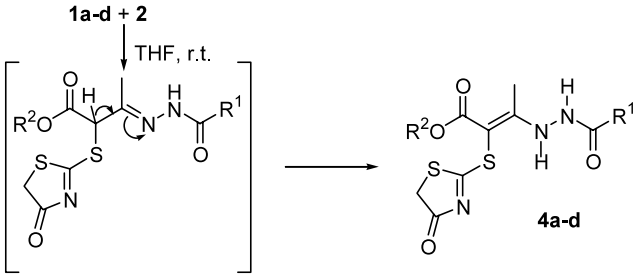
Table 1. Direct synthesis of disulfides **3**

Entry	1	R^1	R^2	3	Yield[a] (%)
1	**1a**	OBn	Me	**3a**	89
2	**1b**	OBu^t	Me	**3b**	85
3	**1c**	OBu^t	Et	**3c**	79
4	**1d**	OMe	Me	**3d**	88
5	**1e**	NHPh	Et	**3e**	75

[a] Yield of pure isolated product.



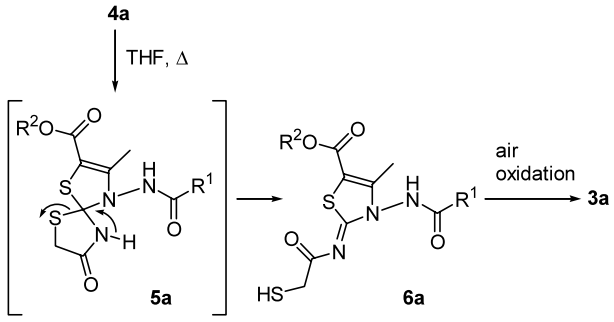
Scheme 2. Synthesis of conjugate adducts **4a**–**d**.

The reaction of 1,2-diaza-1,3-butadienes **1a**–**e** with rhodanine **2** upon reflux in THF (11–13 h) gave in good yields (75–89%) disulfide derivatives **3a**–**e** (Scheme 1; Table 1).

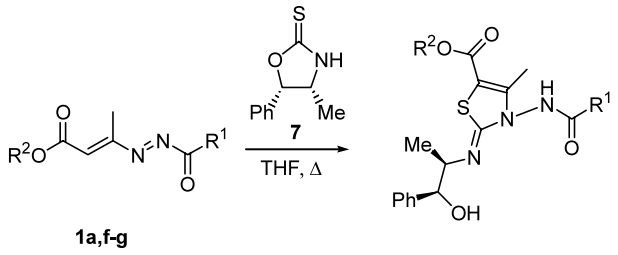
To understand this multi-faceted transformation, we tried the stepwise formation of disulfide **3**. In accordance with our previous results,[8] 1,2-diaza-1,3-butadienes **1a**–**e**[1a] underwent *S*-nucleophilic attack of the thiocarbonyl functionality of rhodanine (**2**) in THF at room temperature (0.5–6 h) to yield the corresponding conjugated 1,4-adducts **4a**–**d**[9] (75–86%) in enamino form (Scheme 2; Table 2).

Any attempt to isolate **4e** met with failure and therefore it was used as crude reaction product. Hence, **4a**–**e** upon reflux in THF until their disappearance (7–15 h) led to disulfide derivatives **3a**–**e**[9] (Table 2).

The hypothesized reaction pathway is shown in Scheme 3. We presumed that an intramolecular *N*-nucleophilic attack at the thioimido moiety of **4a** gives rise to spirocyclic derivative **5a**,[8b] which undergoes ring-opening via imino function formation and C–S bond cleavage to afford thiol derivative **6a** followed by air oxidation to give **3a**.



Scheme 3.



8a: R^1 = OBn, R^2 = Me; 84%

8b: R^1 = NH_2, R^2 = Et; 72%

8c: R^1 = NHPh, R^2 = Me; 65%

Scheme 4.

Evidence for the intermediacy of **6a** was achieved through the ^{1}H NMR spectrum recorded after heating **3a** (48 h) at 90°C in THF-d_8 under an inert atmosphere.[10]

With the aim to extend the scope of our investigation and to obtain more information about the proposed mechanism, we chose an alternative thione incorporating a chiral 1,3-oxazolidine-2-thione moiety. The reaction between 1,2-diaza-1,3-butadienes **1a**,**f**–**g** and (4*R*,5*S*)-(+)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (**7**) after reflux in THF (3–6 h) and subsequent chromatographic purification, gave **8a**–**c** as mixtures of conformers as suggested by dynamic NMR experiments in DMSO-d_6 (293–383 K)[11] (Scheme 4). Probably at room temperature one of the conformers arises by the formation of a hydrogen bond between the hydroxy group and the imino nitrogen, increasing the temperature each pair of signals in ^{1}H NMR spectrum collapse to a single signal.

Table 2. Yields of 1,4-adducts **4** and of the corresponding disulfides **3**

Entry	R^1	R^2	4	Yield[a] (%)	3	Yield[a] (%)
1	OBn	Me	**4a**	86	**3a**	84
2	OBu^t	Me	**4b**	84	**3b**	63
3	OBu^t	Et	**4c**	75	**3c**	67
4	OMe	Me	**4d**	82	**3d**	83
5	NHPh	Et	all **4**		**3e**	67

[a] Yield of pure isolated product.

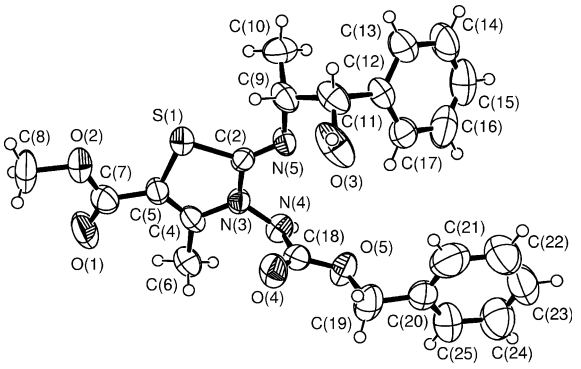


Figure 1. Crystal structure of **8a**. Ellipsoids enclose 50% probability.

The stereochemical assignment was established by single crystal X-ray analysis of **8a** (Fig. 1).

According to this study, **8a**[12] crystallizes in a chiral space group ($P2_1$) suggesting a pure enantiomer. The data show that the two stereogenic carbons have the opposite absolute configuration *R*/*S* or *S*/*R*. Even if there are not very heavy atoms in the molecule, such as bromine, the Flack parameter[13] was refined to 0.07(17), suggesting that the absolute configurations for C(9) and C(11) (see Fig. 1) are *R* and *S*, respectively. It follows that the two stereogenic carbons of starting material (4*R*,5*S*)-(+)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione retain their original configuration in the final product **8a**.

In conclusion the reaction of 1,2-diaza-1,3-butadienes with rhodanine and a similar compound possessing a thioamide function can afford 2-iminothiazoline derivatives through a sequential conjugate addition/annulation/ring-opening reaction. Further work is in progress to evaluate the scope and limitations of this new domino reaction of 1,2-diaza-1,3-butadienes with 2-mercapto-2-thiazoline and oxazolidine-2-thione derivatives bearing a chiral framework.

Acknowledgements

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9. General procedure for the synthesis of Michael adducts (**4a–d**) starting from 1,2-diaza-1,3-butadienes (**1a–d**) and rhodanine (**2**): the appropriate 1,2-diaza-1,3-butadienes **1a–d** (1 mmol) and rhodanine **2** (1 mmol) were dissolved in approximately 20 mL of THF at room temperature until the disappearance of the reagents (0.5–6 h, monitored by TLC). After removal of THF under reduced pressure, compounds **4a–d** were obtained as foams or by crystallization with the appropriate solvents (THF–Et_2O for **4b**; EtOAc/*n*-pentane for **4c**). Data for compound **4a**: mp 129–132°C from EtOAc–light petroleum ether; ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 3.63, (s, 3H, OCH_3), 4.04 (s, 2H, SCH_2), 5.12 (s, 2H, OCH_2), 7.36 (s, 5H, aromatic), 10.05 (b s, 1H, NH), 11.07 (s, 1H, NH); ^{13}C NMR (200 MHz, DMSO-d_6) δ: 16.6 (q), 40.3 (t), 51.8 (q), 66.7 (t), 77.5 (s), 127.9 (d), 128.1 (d), 128.4 (d), 136.2 (s), 155.7 (s), 168.3 (s), 172.5 (s), 189.3 (s), 208.8 (s). IR (Nujol): 3190, 3142, 1734, 1708, 1684, 1661, 1578, 1559 cm^{-1}. Anal. calcd for $C_{16}H_{17}N_3O_5S_2$: C, 48.6; H, 4.33; N, 10.63. Found: C, 48.9; H, 4.1; N, 10.83. General procedure for the synthesis of disulfides (**3a–d**) starting from Michael adducts: the appropriate **4a–d** (1 mmol) was dissolved in 10 mL of THF and heated at reflux until the complete disappearance of the starting materials (7–15 h, monitored by TLC). After removal of the solvent under reduced pressure the crude reaction mixtures were purified by flash chromatography on a silica gel column (eluent, cyclohexane–EtOAc mixtures) to afford **3a–e** that were crystallized from appropriate solvents (EtOAc/*n*-pentane for **3b**; Et_2O–light petroleum ether for **3c**; EtOAc–Et_2O for **3d**; CH_2Cl_2–light petroleum ether for **3e**). Data for compound **3a**: mp 97–100°C from EtOAc–light petroleum ether; ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.47 (s, 6H, 2 CH_3), 3.81 (s, 10H, 2 OCH_3 and 2 SCH_2), 5.17 (d, J=12 Hz, 2H, 2 OCH_aH_b), 5.30 (d, J=12 Hz, 2H, 2 OCH_aH_b), 7.27–7.42 (m, 10H, aromatic), 11.21 (s, 2H, 2 NH); ^{13}C NMR (200 MHz, DMSO-d_6) δ: 11.8 (q), 46.2 (t), 52.5 (q), 67.0 (d), 67.4 (d), 105.9 (s), 127.4 (d), 127.9 (d), 128.5 (d), 135.8 (s), 145.4 (s), 154.1 (s), 155.0 (s), 161.3 (s), 166.4 (s), 178.3 (s). IR (Nujol) 3293, 1747, 1717, 1720, 1601 cm^{-1}; MS *m*/*z*

(API+ESI positive ions) 788.9 $[M+H]^+$, (100). Anal. calcd for $C_{32}H_{32}N_6O_{10}S_4$: C, 48.72; H, 4.09; N, 10.65. Found: C, 48.98; H, 4.27; N, 10.85.

10. ^{1}H NMR (200 MHz, THF-d_8) δ 2.20 (t, $J=7.4$ Hz, 1H, SH), 2.55 (s, 3H, CH_3), 3.33 (d, $J=7.4$ Hz 2H, $COCH_2$), 3.81 (s, 3H, OCH_3) 5.13 (d, $J=12$ Hz, 1H, OCH_aH_b), 5.34 (d, $J=12$ Hz, 1H, OCH_aH_b), 7.31–7.39 (m, 5 H, aromatic), 10.09 (s, 1H, NH).
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12. General procedure for the synthesis of 2-iminothiazoline derivatives (**8a–c**): 1,2-diaza-1,3-butadienes **1a**,**f–g** (1 mmol) and (4*R*,5*S*)-(+)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (**7**) (1 mmol) were dissolved in approximately 20 mL of THF at room temperature until the disappearance of the reagents (1–2 h, monitored by TLC). Then, the reaction mixtures were heated at reflux (2–4 h). After removal of THF under reduced pressure, compounds **8a–c** were purified by flash-chromatography on a silica-gel column (eluent, cyclohexane–EtOAc mixtures) and subsequent crystallization with the appropriate solvents (EtOAc/Et_2O for **8b**; THF/*n*-pentane for **8c**. Data for compound **8a**: mp 120–122°C from Et_2O/*n*-pentane; ^{1}H NMR (200 MHz, DMSO-d_6) δ: 0.98 and 1.01 (2×d, $J=6$ Hz, 3H, CH_3), 2.24 and 2.28 (2×s, 3H, CH_3), 3.02–3.09 (m, 1H, CH), 3.68 (s, 3H, OCH_3), 4.35–4.40 (m, 1H, CH), 5.10–5.19 (m, 3H, OCH_2 and OH), 7.17–7.42 (m, 10H, aromatic), 9.79 and 10.19 (2×bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 12.2, 16.7, 17.1, 51.9, 65.6, 66.0, 66.8, 76.2, 76.9, 95.1, 126.5, 126.7, 127.1, 127.3, 127.4, 127.5, 127.8, 128.5, 136.1, 143.1, 143.4, 148.1, 151.3, 155.3, 155.6, 161.6; IR 3310, 3218, 1732, 1709, 1645, 1604 cm^{-1}; MS *m*/*z* 456 (M^++1, 22), 438 (9), 424 (45), 349 (100). Anal. calcd for $C_{23}H_{25}N_3O_5S$: C, 60.64; H, 5.53; N, 9.22. Found: C, 60.96; H, 5.28; N, 9.02. Crystal data: monoclinic, space group $P2_1$ (n. 4) $a=14.190(2)$, $b=4.9282(8)$, $c=16.923(2)$ Å, $\beta=99.669(10)°$, $V=1166.6(3)$Å^3, $Z=2$; R_1 ($I>2\sigma(I)$) $=0.055$, $wR_2(I>2\sigma(I))=0.098$. Additional crystallographic data (excluding structures factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-213837. Copies of the data can be obtain, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code +44-(1223)336-033 or e-mail: deposit@ccdc.cam.ac.uk].
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