Direct Access to Variously Substituted 2-Imino-4-thiazolines

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Abstract: 1,2-Diaza-1,3-dienes readily react as Michael acceptors with thiocyanic acid generated in situ from potassium thiocyanate. The acidic medium of the reaction promotes the intramolecular ring closure of the α-thiocyanato hydrazones allowing access to novel 2-imino-4-thiazolines functionalized at positions 3, 4, and 5 in a one-pot, high-yielding process.

Key words: 1,2-diaza-1,3-dienes, thiocyanation, Michael addition, ring closure, 2-imino-4-thiazoline, heterocycles

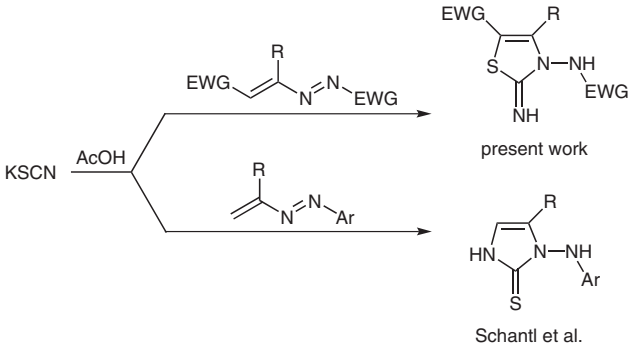
The chemistry of 1,2-diaza-1,3-dienes has been under active investigation by several groups for a number of years.[1] Depending on the nature of the substituents present both at the olefinic moiety and at the azo group, as well as on the reagent, this class of intermediates is capable of participating in cycloaddition reactions[2] or nucleophilic additions.[3] From our experience,[3a,b] electron-withdrawing groups on the terminal carbon and/or nitrogen atom increase the electrophilic character of the heterodiene system making conjugated azoalkenes good Michael acceptors. Since the resulting Michael adducts bear suitable nucleophilic and electrophilic features, a cyclization reaction can follow the addition step to produce functionalized heterocycles. In this context, by using variously functionalized *S*-nucleophiles, we have previously reported the synthesis of 2-phenylimino-4-thiazoline[4] and 2-alkylimino-4-thiazoline derivatives.[5]

In view of the fact that 2-imino-4-thiazolines demonstrate a range of biological effects such as antimicrobial, anti-inflammatory, antihistaminic, antihypertensive, and hypnotic activity, as well as positive myeloperoxidase reactivity,[6] we were interested in their synthesis.

In the literature, several strategies for the synthesis of 2-iminothiazoline are known. The first reports on the synthesis of 2-imino-4-thiazoline, published more than a century ago, comprise a condensation reaction of α-haloketones with thiourea, in neutral or basic medium (Hantzsch synthesis) or with ammonium thiocyanate; both methods suffering from the drawback isomer formation.[7] The same condensation reactions under acidic conditions give rise to 2-imino-4-thiazolines in addition to variable amounts of aminothiazoles as side products.[8] At present the best entries to the 2-imino-4-thiazoline system involve alkylation of 2-aminothiazoles obtained from the condensation of α-haloketone with thiourea, or the reaction of α-bromoketimines with potassium thiocyanate.[9] This latter method is limited to substrates having an alkyl substituent at the 3- and the 5-position, and an aromatic substituent at the 4-position; whereas this letter reports an efficient and straightforward one-pot synthesis of 2-imino-4-thiazolines variously functionalized at all the three positions.

Based on our experience[4,5,10] and on the results obtained by Yadav on chalcones,[11] we decided to investigate an approach based on conjugate hydrothiocyanation of suitable heterodiene systems from which to drive an intramolecular ring closure and achieve our target.

Since the reaction of in situ generated conjugated phenylazoalkenes and thiocyanic acid is reported to give rise to 2,3-dihydro-1*H*-imidazole-2-thione derivatives by [3+2] cycloaddition,[12] we postulated that the introduction of electron-withdrawing substituents, both on the olefinic moiety and at the azo group of the azo–ene system, could influence the outcome of that reaction (Scheme 1).



Scheme 1

Indeed, the treatment of 1,2-diaza-1,3-dienes **1a–k** with KSCN (**2**), in glacial acetic acid at room temperature, immediately produced Michael adducts **3**. We predicted that the acidic conditions could promote the activation of the cyano functionality of the α-thiocyanato hydrazones **3** towards ring closure and, in fact, **3** was completely converted into the desired 2-imino-4-thiazoline derivatives **4a–k** (67–93%)[13] on standing in acidic medium for several hours (Scheme 2, Table 1).

From a mechanistic point of view (Scheme 2) and in accordance with our previous results, we propose that the formation of **4** arises from nucleophilic addition of the sulfur atom of thiocyanate anion at the terminal carbon of

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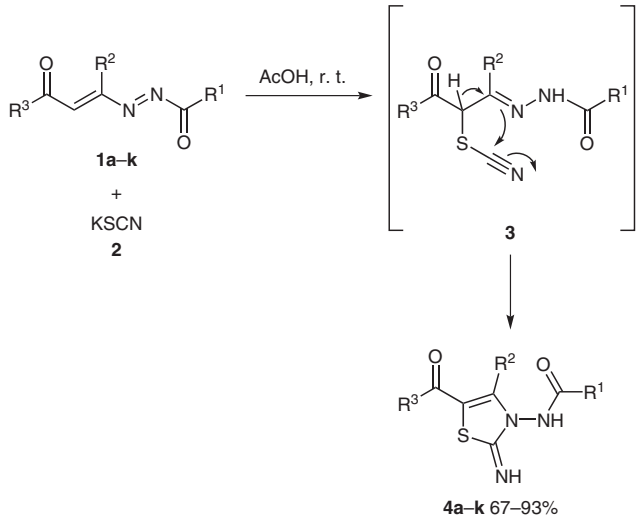
the activated olefinic moiety to produce **3** followed by intramolecular nucleophilic attack of the hydrazone sp^2-nitrogen across the carbon–nitrogen triple bond. In support of this, using **1j** allowed us to characterize **3j**[14] as a stable α-thiocyanato hydrazone derivative and to follow its conversion into **4j**[15] upon treatment with acetic acid.



Scheme 2

Table 1 Results of the Synthesis of 2-Imino-4-thiazolines **4a–k**

Entry	1,3-Diaza-1,3-diene **1**	R^1	R^2	R^3	2-Imino-4-thiazoline **4**	Yield (%)[a]
1	**1a**	O*t*-Bu	Me	OEt	**4a**	91
2	**1b**	O*t*-Bu	Me	OMe	**4b**	93
3	**1c**	OMe	Me	OBn	**4c**	91
4	**1d**	NH_2	Me	OEt	**4d**	72
5	**1e**	O*t*-Bu	Et	OMe	**4e**	78
6	**1f**	NHPh	Me	NMe_2	**4f**	74
7	**1g**	OBn	Et	OMe	**4g**	84
8	**1h**	OMe	Me	OEt	**4h**	85
9	**1i**	OEt	Me	OEt	**4i**	92
10	**1j**	O*t*-Bu	Me	NMe_2	**4j**	72
11	**1k**	NH_2	Me	OMe	**4k**	67

[a] Yield of pure isolated product in one-pot procedure.

In summary, conjugate hydrothiocyanation of 1,2-diaza-1,3-dienes in acidic medium offers an efficient one-pot synthetic approach to novel 2-imino-4-thiazolines variously substituted at 3-, 4-, and 5-position. The nature of substituents at the 1- and 4-positions of the conjugate azo–ene system plays a key role in driving the process through nucleophilic interactions without any isomerization of the α-thiocyanato hydrazone intermediate in contrast to results obtained by other groups for similar reactions.[12]

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(13) **Typical One-Pot Procedure for the Preparation of 2-Imino-4-thiazoline Derivatives 4a–k**
The requisite 1,2-diaza-1,3-butadiene **1a–k** (1 mmol), prepared and used as an *E*,*E*/*E*,*Z* isomer mixture,[1c] was added to a solution of KSCN (106.7 mg, 1.1 mmol) in glacial AcOH (2 mL) under magnetic stirring. The consumption of

1a–**k** was rapid and TLC analysis indicated the presence one major product. The reaction mixture was allowed to stand at r.t. overnight to allow complete conversion of the Michael adduct into the corresponding 2-imino-4-thiazoline derivative. AcOH was removed in vacuo, the residue was dissolved in H_2O, and the solution neutralized with sat. Na_2CO_3. Compounds **4a**–**c**,**e**,**g**–**i** were obtained by extraction of the aqueous phase with Et_2O. The dried organic layers were filtered and evaporated, and the crude compounds were isolated as powders or foams and purified by recrystallization or by flash chromatography on silica. Compounds **4d**,**f**,**j**,**k**, precipitated from the aqueous medium after addition of sat. Na_2CO_3 and were isolated by filtration and recrystallized from an appropriate solvent mixture

(14) **Data for *tert*-Butyl-2-[3-(dimethylamino)-1-methyl-3-oxo-2-thiocyanatopropylidene]hydrazinecarboxylate (3j)**
White powder from EtOAc–cyclohexane; mp 139–140 °C (dec.). IR (KBr): 3467, 3331, 2153, 1746, 1650, 1503 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.45 (s, 9 H, O*t*-Bu), 1.86 (s, 3 H, CH_3), 2.86 and 2.97 [2 s, 6 H, $N(CH_3)_2$], 5.79 (s, 1 H, CH), 10.00 (s, 1 H, NH). ^{13}C NMR (100 MHz DMSO-d_6): δ = 12.3 (q), 28.0 (q), 35.9 (q), 37.1 (q), 61.0 (d), 79.8 (s), 112.4 (s), 144.9 (s), 152.6 (s), 164.7 (s). ESI-MS: *m/z* calcd for $C_{12}H_{20}N_4O_3S$: 300.4; found: 301 [M + 1].

(15) **Data for *tert*-Butyl {5-[(Dimethylamino)carbonyl]-2-imino-4-methyl-1,3-thiazol-3 (2*H*)-yl}carbamate (4j)**
White powder from EtOAc–cyclohexane; mp 159–160 °C (dec.). IR (KBr): 3318, 3255, 3203, 1736, 1631, 1606 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.38 and 1.43 (2 s, 9 H, O*t*-Bu), 1.89 (s, 3 H, CH_3), 2.93 [s, 6 H, $N(CH_3)_2$], 8.18 (br s, 1 H, NH), 9.64 (br s, 1 H, NH). ^{13}C NMR (100 MHz DMSO-d_6): δ = 12.7 (q), 27.6 and 27.8 (2 q), 36.6 (q), 40.1 (q), 80.5 (s), 98.5 (s), 136.9 (s), 154.6 (s), 157.9 (s), 162.8 (s). ESI-MS: *m/z* calcd for $C_{12}H_{20}N_4O_3S$: 300.4; found: 301 [M + 1].