A New Convenient Preparation of 2-, 4-, and 5-Thiazolecarboxaldehydes and Their Conversion into the Corresponding Carbonitrile *N*-Oxides: Synthesis of 3-Thiazolylisoxazoles and 3-Thiazolylisoxazolines

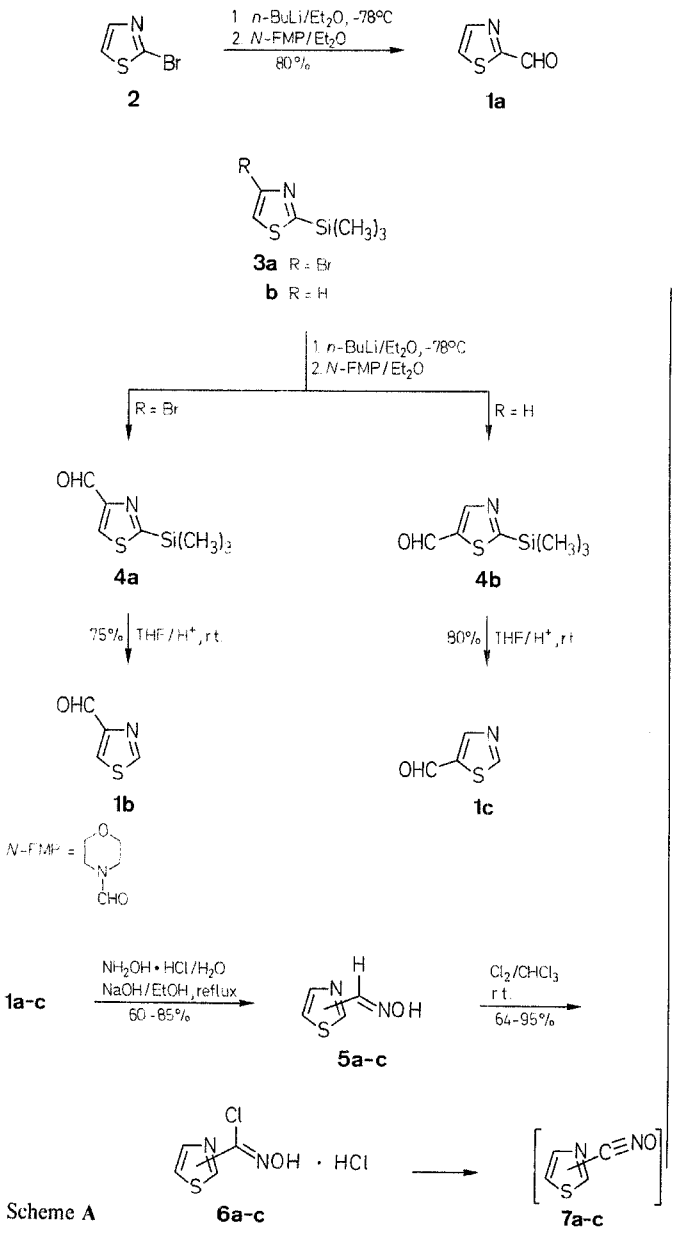
Alessandro Dondoni,* Giancarlo Fantin, Marco Fogagnolo, Alessandro Medici, Paola Pedrini

Dipartimento di Chimica, Laboratorio di Chimica Organica, Università di Ferrara, via L. Borsari 46, I-44100 Ferrara, Italy

The title aldehydes are prepared in high yields by quenching 2-lithiothiazole, 4-lithio-, and 5-lithio-2-trimethylsilylthiazole with *N*-formylmorpholine followed by protodesilylation in the latter two cases. The aldehydes are transformed through their oximes and hydroxamoyl chlorides into nitrile oxides which react with alkene and acetylene dipolarophiles to give 3-thiazolylisoxazolines and 3-thiazolylisoxazoles in moderate to good yields.

The use of thiazolecarboxaldehydes as auxiliaries in synthesis and precursors to thiazole containing complex molecular systems has been somewhat limited because of the lack of convenient preparative methods of these simple compounds.[1] For instance thiazole 2-carboxaldehyde (**1a**) is the most readily available regioisomer which however has been prepared in modest yields from 2-lithiothiazole and *N*-methylformanilide (30%)[2] or dimethylformamide (61%).[3] The same approach does not apply to 4- and 5-regioisomers **1b** and **1c** for which there are unexemplified patented procedures based on catalytic oxidation of alkylthiazoles[4] and cyclization between bromomalonodialdehyde and thiocarbamide.[5] While in connection with our studies on thiazoles as synthetic auxiliaries[6] we needed high yield entries to aldehydes **1a–c**, we decided to examine their preparation from the corresponding lithiothiazoles using *N*-formylmorpholine (*N*-FMP)[7] as a formylating agent.

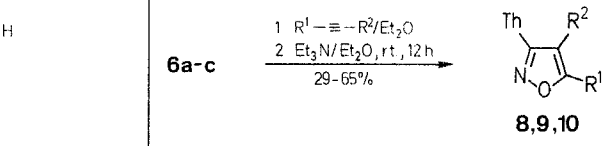
Quenching 2-lithiothiazole generated from 2-bromothiazole (**2**) and *n*-butyllithium at −78 °C with *N*-FMP and keeping the reaction mixture overnight at −15 °C produced the aldehyde **1a** in 80% yield. Interestingly enough, a similar yield (78%) was obtained using dimethylformamide as a formylating agent. The selective lithiation at C-4 and C-5 of the thiazole ring was achieved by our simple strategy[8] consisting of the use of the trimethylsilyl group as a blocking yet easily removable group at C-2. Thus on treating 2-trimethylsilyl-4-bromothiazole (**3a**) with *n*-butyllithium at −78 °C and then quenching with *N*-FMP afforded exclusively (NMR) 2-trimethylsilyl-4-formylthiazole (**4a**), which was conveniently desilylated upon acidic work-up into 4-thiazolecarboxaldehyde (**1b**) in 75% yield. In a similar way the regioisomer **1c** was obtained in 80% yield from 2-trimethylsilylthiazole **3b** through the intermediate **4b** (Scheme A). The use of *N*-FMP appeared essential for high yield formylation, since DMF gave lower yields of both **1b** (15%) and **1c** (40%). The ease of the reactions described above and the mild conditions, giving excellent preparative yields, together with the ready availability of reagents, make this formylating procedure of thiazole ring at 4- and 5-position the method of choice among those so far reported.



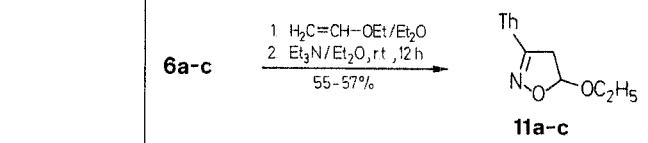
Scheme A

With a ready source of thiazole aldehydes **1a–c** at hand, we sought the possibility of simple elaborations of the formyl group into other reactive functionalities of synthetic utility. To this end, the preparation of thiazole carbonitrile *N*-oxides **7a–c** from aldehydes **1a–c** by CHO into C≡NO transformation appeared to be both straightforward and appealing since nitrile oxides constitute one of the most versatile class of 1,3-dipolar systems,[9] whose participation in intra- and intermolecular cycloaddition reactions with various dipolarophiles has been amply exploited in natural products synthesis.[10–12]

Thus the classical sequence for nitrile oxides preparation[13] from aldehydes, *viz.* oximation, chlorination, and dehydrochlorination, was followed to transform **1a–c** into nitrile oxides **7a–c**. However, compounds **7a–c** were not isolated as pure materials because of their conversion at room temperature into various products, very likely dimers and polymers. This is a quite common behaviour of many unstable nitrile oxides.[13] Instead nitrile oxides **7a–c** were conveniently generated *in situ* from the corresponding hydroxamoyl chlorides hydrochlorides **6a–c** in the presence of suitable alkene and acetylene dipolarophiles. In all cases the corresponding cycloadducts, *viz.* isoxazoles **8a, 8b, 9a, 10a**, and **10c** and isoxazolines **11a–c**, with the expected regiochemistry (Scheme B) were obtained in moderate to good yields (Table). Isoxazoles and isoxazolines with a thiazole ring as a substituent at the 3-position have not been reported so far. Particularly attractive are thiazol-2-yl derivatives **8a–10a** and **11a**, which, because of the thiazole-formyl equivalence,[14] are masked 3-isoxazole and 3-isoxazoline carboxaldehydes, a class of valuable substrates for amino sugar synthesis.[15] Hence compounds **8–11** and others which may be similarly prepared with different substituents at 4- and 5-position, have their own importance as coupled diheterocyclic systems[8,16] or may be employed as precursors to acyclic systems by protocols combining the isoxazole[17] or isoxazoline ring[11,12,18] opening with the deblocking of the formyl group from the thiazole ring.[19]



	Th	R^1	R^2
8a	2-thiazolyl	$CO_2C_2H_5$	H
9a	2-thiazolyl	OC_2H_2	H
10a	2-thiazolyl	$Si(CH_3)_3$	$Si(CH_3)_3$
8b	4-thiazolyl	$CO_2C_2H_5$	H
10c	5-thiazolyl	$Si(CH_3)_3$	$Si(CH_3)_3$



11	Th
a	2-thiazolyl
b	4-thiazolyl
c	5-thiazolyl

Scheme B

All reactions are carried out under nitrogen using anhydrous solvents. 2-Trimethylsilyl-4-bromothiazole (**3a**)[8] and 2-trimethylsilylthiazole (**3b**)[20] are prepared as described.

Table. Cycloadducts **8**–**11** Prepared

Product	Yield[a] (%)	m.p. (°C)	Molecular Formula[b]	IR (Solvent)[c] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)	MS (70 eV)[e] m/e (M^+)
8a	65	88–90	$C_9H_8N_2O_3S$ (224.2)	1810, 1670 (CCl_4)	1.44 (t, 3H, J = 8); 4.47 (q, 2H, J = 8); 7.47 (s, 1H); 7.51 (d, 1H, J = 3.4); 7.96 (d, 1H, J = 3.4)	224
9a	65	oil	$C_8H_8N_2O_2S$ (196.2)	1605 (Film)	1.47 (t, 3H, J = 8); 4.32 (q, 2H, J = 8); 5.83 (s, 1H); 7.5 (d, 1H, J = 3.4); 7.95 (d, 1H, J = 3.4)	196
10a	36	oil	$C_{12}H_{20}N_2OSSi_2$ (296.5)	1485 (Film)	0.27 (s, 9H); 0.37 (s, 9H); 7.41 (d, 1H, J = 3.4); 7.92 (d, 1H, J = 3.4)	296
8b	62	84–85	$C_9H_8N_2O_3S$ (224.2)	1740 (CCl_4)	1.43 (t, 3H, J = 7.2); 4.46 (q, 2H, J = 7.2); 7.43 (s, 1H); 8.05 (d, 1H, J = 2.2); 8.93 (d, 1H, J = 2.2)	224
10c	29	oil	$C_{12}H_{20}N_2OSSi_2$ (296.5)	1490 (Film)	0.18 (s, 9H); 0.46 (s, 9H); 7.95 (s, 1H); 8.86 (s, 1H)	296
11a	55	oil	$C_8H_{10}N_2O_2S$ (198.2)	1490 (Film)	1.21 (t, H, J = 7); 3.46 (m, 2H); 3.75 (q, 2H, J = 7); 5.75 (m, 1H); 7.38 (d, 1H, J = 3.4); 7.85 (d, 1H, J = 3.4)	198
11b	57	74–75	$C_8H_{10}N_2O_2S$ (198.2)	1470 (Nujol)	1.22 (t, 3H, J = 7.4); 3.46 (m, 2H); 3.77 (q, 2H, J = 7.4); 5.7 (m, 1H); 7.86 (d, 1H, J = 2); 8.82 (d, 1H, J = 2)	198
11c	55	oil	$C_8H_{10}N_2O_2S$ (198.2)	1480 (Film)	1.22 (t, 3H, J = 7); 3.35 (m, 2H); 3.77 (q, 2H, J = 7); 5.71 (m, 1H); 7.97 (d, 1H, J = 1); 8.85 (d, 1H, J = 1)	198

[a] After chromatography.
[b] Satisfactory microanalyses obtained: C ±0.27, H ±0.26, N ±0.15
[c] Recorded on a Perkin-Elmer 297 Infrared spectrophotometer.
[d] Obtained on a Bruker WP 80 spectrometer.
[e] Recorded on a Varian MAT CH7 spectrometer.

Thiazole-2-carboxaldehyde (1a):
To a stirred and cooled (−78°C) 1.5 M solution of BuLi in *n*-hexane (41 mL, 61.8 mmol) diluted with ether (100 mL) is added dropwise in 1 h a solution of 2-bromothiazole (**2**; 10 g, 60 mmol) in ether (50 mL). The mixture is stirred at −78°C for 1 h and then a solution of *N*-formylmorpholine (6.1 mL, 60 mmol) in ether (30 mL) is added dropwise in 15 min. After 1 h at −78°C and 18 h at −15°C, the reaction mixture is extracted with 4 normal HCl (4 × 20 mL). The aqueous layers are combined, treated with solid $NaHCO_3$ (pH 9), and then extracted with ether (4 × 40 mL). The organic layer is dried (Na_2SO_4), filtered and the solvent is removed under vacuum. Distillation of the residue gives the aldehyde **1a**; yield: 5.42 g (80%); b.p. 61–63°C/15 mbar (Lit.[3], 62–64°C/15 mbar).

IR (Film): ν = 1700 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 7.71 (dd, 1H, J = 2, 3.2 Hz); 8.07 (d, 1H, J = 3.2 Hz); 9.95 (d, 1H, J = 2 Hz).

Thiazole-4-carboxaldehyde (1b):
To a stirred and cooled solution (−78°C) of 1.5 M BuLi in *n*-hexane (20 mL, 29.9 mmol) diluted with ether (50 mL) is added dropwise in 1 h a solution of 2-trimethylsilyl-4-bromothiazole (**3a**; 4.7 g, 19.9 mmol) in ether (20 mL). The mixture is stirred at −78°C for 30 min and then a solution of *N*-formylmorpholine (3 mL, 29.9 mmol) in ether (30 mL) is added dropwise in 15 min. After 30 min at −78°C, the mixture is washed with saturated aqueous $NaHCO_3$ (30 mL) and extracted with ether (2 × 20 mL). The organic layer is dried (Na_2SO_4) and the solvent is removed under vacuum to give the crude 4-formyl-2-trimethylsilylthiazole (**4a**); yield: 2.9 g (80%); oil.

$C_7H_{11}NOSSi$ (185.3)	calc.	C 45.37	H 5.98	N 7.56
	found	45.40	5.95	7.54

IR (Film): ν = 1700 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.45 (s, 9H); 8.31 (s, 1H); 10.15 (s, 1H).

MS (70 eV): m/e = 185 (M^+), 170, 115.

The crude product **4a** (2.9 g) is dissolved in THF (30 mL) and 1 normal HCl (1 mL) is added under stirring. After 1 h, the solvent is removed *in vacuo*, the residue is diluted with water (20 mL) and extracted with ether (3 × 20 mL). The organic layer is dried (Na_2SO_4) and the solvent removed under vacuum. Chromatography on silica gel (eluent: EtOAc/*n*-hexane, 1:1) gives the aldehyde **1b**; yield: 1.7 g (75% based on starting thiazole **3a**); m.p. 62–64°C (Lit.[21] 63–65°C).

^{1}H-NMR ($CDCl_3$/TMS): δ = 8.25 (d, 1H, J = 1.9 Hz); 8.91 (d, 1H, J = 1.9 Hz); 10.14 (s, 1H).

MS (70 eV): m/e = 113 (M^+), 85.

Thiazole-5-carboxaldehyde (1c):
To a stirred and cooled solution (−78°C) of BuLi (22.8 mmol) in ether (80 mL) is added dropwise in 1 h a solution of 2-trimethylsilylthiazole (**3b**; 3.5 g, 22.3 mmol) in ether (20 mL). The mixture is stirred at −78°C for 30 min, then a solution of *N*-formylmorpholine (2.45 mL, 24.5 mmol) in ether (20 mL) is added dropwise. The reaction mixture is worked up as above for **1b** to give the crude **4b**; yield: 4 g (97%); oil.

$C_7H_{11}NOSSi$ (185.3)	calc.	C 45.37	H 5.98	N 7.56
	found	45.34	5.99	7.53

IR (Film): ν = 1690 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.44 (s, 9H); 8.56 (s, 1H); 10.04 (s, 1H).

MS (70 eV): m/e = 185 (M^+), 170, 115.

The crude product **4b** is treated with 1 normal HCl (2 mL) in THF (30 mL) for 2 h. The mixture is worked up as above for **4a**. Chromatography on silica gel (eluent: EtOAc/*n*-hexane, 1:1) gives the aldehyde **1c**; yield: 2 g (80% based on the starting thiazole **3b**); m.p. 92–94°C (Lit.[21] 90–94°C).

^{1}H-NMR ($CDCl_3$/TMS): δ = 8.48 (s, 1H); 9.06 (s, 1H); 10.06 (s, 1H).

MS (70 eV): m/e = 113 (M^+), 84.

Oximes 5a–c; General Procedure:
To a solution of thiazole carboxaldehyde **1** (2 g, 17.7 mmol) in EtOH (50 mL), a solution of $NH_2OH \cdot HCl$ (5 g, 72 mmol) in water (20 mL) and an aqueous solution of 20% NaOH (20 mL) are added. The mixture is refluxed for 40 min. The solvent is removed under vacuum and the residue is diluted with water until the oxime **5** precipitates.

5a; yield: 1.8 g (79%); m.p. 118–120°C (Lit.[3] 117°C).

5b; yield: 1.35 g (60%); m.p. 185–186°C.

$C_4H_4N_2OS$ (128.2)	calc.	C 37.49	H 3.15	N 21.86
	found	37.51	3.14	21.89

^{1}H-NMR (CD_3OD-D_2O/TMS): δ = 7.81 (d, 1H, J = 1.7 Hz); 8.26 (s, 1H); 8.98 (d, 1H, J = 1.7 Hz).

5c; yield: 1.92 g (85%); m.p. 197–198°C.

$C_4H_3N_2OS$: calc. C 37.49 H 3.15 N 21.86
(128.2) found 37.46 3.16 21.85

^{1}H-NMR (CD_3OD-D_2O/TMS): δ = 7.87 (s, 1H); 8.22 (s, 1H); 9.06 (s, 1H).

Hydroxamoyl Chlorides Hydrochlorides 6a–c; General Procedure:
To a stirred solution of chlorine (0.2 g, 2.89 mmol) in $CHCl_3$ (100 mL) is added dropwise a solution of the oxime **5** (0.37 g, 2.89 mmol) in $CHCl_3$ (60 mL). After 12 h the hydroxamoyl chloride hydrochloride **6** is filtered off.

6a; yield: 0.54 g (95%); m.p. 153–155°C (dec).

$C_4H_4Cl_2N_2OS$: calc. C 24.13 H 2.02 N 14.07
(199.1) found 24.10 2.01 14.05

^{1}H-NMR (CD_3OD/TMS): δ = 5.33 (br, 2H), 7.9 (d, 1H, J = 3.4 Hz), 8.06 (d, 1H, J = 3.4 Hz).

6b; yield: 0.37 g (64%); decomposes at ca. 250°C.

$C_4H_4Cl_2N_2OS$: calc. C 24.13 H 2.02 N 14.07
(199.1) found 24.14 2.01 14.08

^{1}H-NMR (Acetone-d_6/TMS): δ = 8.03 (d, 1H, J = 2 Hz), 9.08 (d, 1H, J = 2 Hz).

6c; yield: 0.43 (94%); m.p. 210–212°C (dec).

$C_4H_4Cl_2N_2OS$: calc. C 24.13 H 2.02 N 14.07
(199.1) found 24.11 2.00 14.05

^{1}H-NMR (CD_3OD/TMS): δ = 8.5 (s, 1H), 9.64 (s, 1H).

Cycloaddition Reactions; General Procedure:
To a stirred suspension of hydroxamoyl chloride hydrochloride **6** (0.2 g, 1 mmol) and the appropriate dipolarophile (5 mmol) in ether (30 mL) is added in 4–5 h a solution of triethylamine (0.2 g, 2 mmol) in ether (40 mL). After 10–12 h additional stirring, the mixture is washed with water (2 × 20 mL) and then dried (Na_2SO_4). The solvent is removed under vacuum and the residue chromatographed on silica gel (eluent: CH_2Cl_2/EtOAc; 9:1) to give the cycloadducts **8–11** (Table).

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