A Novel Method of Synthesis of 2-Methylthio-1,3-oxazoles

Carlos Alvarez-Ibarra,* Magnolia Mendoza, Guillermo Orellana, Maria L. Quiroga

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, Ciudad Universitaria, s/n, E-28040 Madrid, Spain

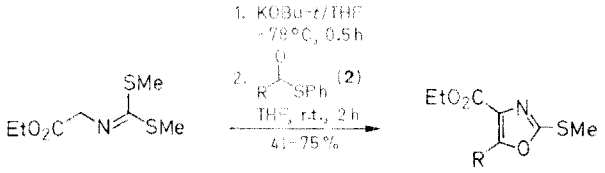
A one-pot synthesis of 2-methylthio-1,3-oxazoles by a cyclocondensation reaction between dimethyl *N*-(ethoxycarbonylmethyl)iminodithiocarbonate and *S*-phenyl alkanethioates and thiobenzoates is described. The new procedure offers several advantages: easy access of the reagents, high selectivity, and facile introduction of different substitutions in the heterocyclic ring.

A simple preparation of 2-methylthio-1,3-oxazoles is of considerable interest because of the wide synthetic applications of these heterocyles,[1,2] which include the construction of carbon–carbon bonds by using transition metal complexes as catalysts,[3–5] and the possible transformations into other derivatives through transfunctionalization reactions.[6–8]

To our knowledge, the route to the oxazole ring by consecutive or simultaneous buildup of its O(1)-C(2) and C(4)-C(5) bonds has not led to the introduction of the 2-methylthio group.[9–13] The cyclocondensation reaction between aldehydes and dimethyl tosylmethyliminodithiocarbonate to 2-methylthio-1,3-oxazoles is reported to be unsuccessful.[14]

In this paper we describe a new procedure of synthesis of 2-methylthio-1,3-oxazoles, which follows the former route and involves a cyclocondensation reaction between the azaallylic anion derived from dimethyl *N*-(ethoxycarbonylmethyl)iminodithiocarbonate (**1**) and *S*-phenyl alkanethioates and thiobenzoates **2**.

Selectivity and applicability of the method has been tested, and the new 5-alkyl- and 5-aryl-4-ethoxycarbonyl-2-methylthio-1,3-oxazoles **3** are obtained by this simple procedure with acceptable yields (Table 1).



1 **3a–g**

2, 3	R	2, 3	R
a	Ph	**e**	CH_3
b	$4\text{-}CH_3C_6H_4$	**f**	$(CH_3)_3CH_2$
c	$4\text{-}ClC_6H_4$	**g**	$PhCH_2$
d	$3\text{-}ClC_6H_4$		

Aromatic *S*-phenyl thiocarboxylates **2a–d** are prepared in excellent yields (> 80%) by following the method of Dalgliesh and Mann.[15] This procedure involves the reaction between an acyl chloride and the thiophenol anion in aqueous solution. The best method for the synthesis of aliphatic *S*-phenyl thiocarboxylates **2e–g** has been the reaction between the appropriate carboxylic acid and 1,1'-carbonyldiimidazole, followed by the *in situ* addition of thiophenol as reported by Staab.[16] In this way, thiocarboxylates **2e–g** are obtained in good yields (66–81%) and with an adequate grade (> 98%, GLC) for subsequent use without further purification.

Preparation of dimethyl *N*-(ethoxycarbonylmethyl)iminodithiocarbonate[17] from glycine ethyl ester hydrochloride and metalation of the former with potassium *tert*-butoxide has been previously reported.[18,19] Other iminodithiocarbonates lead to 2-methylthio-1,3-oxazoles with a different substituent at C-4 (e.g. phenyl[20]) which can be used to study their reactivity with reagents that are incompatible with an ester group in the molecule.

Unequivocal characterization of the 1,3-oxazoles **3** follows from the NMR and MS data (Table 2). Only for the 1,3-oxazoles **3e** and **3f**, which lack of phenyl group, the multiplicity of ^{13}C-NMR signals can be clearly observed in the proton-coupled spectra. The NMR carbon–proton coupling constants are instructive in the determination of the regiochemistry of the product. For instance, the 2-methylthio-1,3-oxazole **3e** shows ^{13}C-NMR key resonances as follows: 159.1 (q, $^3J_{CH} = 5.7$ Hz, C-2); 156.8 (q, $^2J_{CH} = 7.4$ Hz, C-5); 128.4 (q, $^3J_{CH} = 3.4$ Hz, C-4). The observed coupling constants are in close agreement with those values of similar 2-methylthio-1,3-thiazoles previously reported.[18,19] In addition, the ^{13}C chemical shifts of C-2, C-5, and C-4 of the novel 1,3-oxazole rings of **3** are comparable to those calculated from the data of 1,3-oxazole and 5-(4-chlorophenyl)-1,3-oxazole reported by van Leusen *et al.*[21]

Glycine ethyl ester hydrochloride, thiophenol, carboxylic acids, and acyl chlorides have been purchased from Aldrich. KOBu-*t* and 1,1'-carbonyldiimidazole were obtained from Merck. Reagent quality solvents have been used without further purification. THF was freshly distilled over $LiAlH_4$. Analytical and preparative TLC plates and silica gel (230–400 mesh) have been purchased from Merck. Melting points were determined using a Büchi apparatus and are uncorrected. Microanalytical data were obtained in the Centro de Investigacion y Desarrollo CSIC (Barcelona, Spain).

Table 1. 2-Methylthio-1,3-oxazoles **3** Obtained by Cyclocondensation of **1** with *S*-Phenyl Thiocarboxylates **2**

Product	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c]	IR[d] ν(cm^{-1})	MS[e] *m/z* (%)
3a	56	84–86 (ligroin)	$C_{13}H_{13}NO_3S$ (263.3)	3080, 1690, 1580, 1510, 1215, 1080	263 (M^+, 100); 264 ($M^+ + 1$, 14.2); 265 ($M^+ + 2$, 6.0); 188 ($M^+ - OCSCH_3$, 55); 105 (arylacylium, 74); 75 (CH_3SCO^+, 52)
3b	75	68–69 (pentane)	$C_{14}H_{15}NO_3S$ (277.3)	2980, 1710, 1575, 1500, 1170, 1070	277 (M^+, 100); 278 ($M^+ + 1$, 16.5); 279 ($M^+ + 2$, 6.1); 119 (arylacylium, 59); 75 (CH_3SCO^+, 24)
3c	55	86–87 (ligroin)	$C_{13}H_{12}ClNO_3S$ (297.7)	2980, 1705, 1605, 1500, 1170, 1075	297 (M^+, 100); 298 ($M^+ + 1$, 16.5); 299 ($M^+ + 2$, 38.8); 222 ($M^+ - OCSCH_3$, 45); 139 (arylacylium, 57); 75 (CH_3SCO^+, 61)
3d	55	66–67 (ligroin)	$C_{13}H_{12}ClNO_3S$ (297.7)	3110, 1705, 1585, 1505, 1200, 1090	297 (M^+, 100); 298 ($M^+ + 1$, 17.2); 299 ($M^+ + 2$, 39.3); 222 ($M^+ - OCSCH_3$, 61); 139 (arylacylium, 61); 75 (CH_3SCO^+, 89)
3e[f]	48	oil	$C_8H_{11}NO_3S$ (201.2)	2995, 1705, 1620, 1510, 1175, 1085	203 ($M^+ + 2$, 1.0); 136 ($M^+ - H_2O - SCH_3$, 100); 75 (CH_3SCO^+, 28); 43 (acetylium, 6)
3f[f]	41	oil	$C_{12}H_{19}NO_3S$ (257.3)	2950, 1710, 1605, 1510, 1165, 1060	257 (M^+, 20.6); 258 ($M^+ + 1$, 3.1); 259 ($M^+ + 2$, 1.5); 155 ($M^+ - NCSCH_3 - C_2H_5$, 100); 75 (CH_3SCO^+, 15)
3g[f]	53	oil	$C_{14}H_{15}NO_3S$ (277.3)	3060, 1710, 1615, 1505, 1170, 1060	277 (M^+, 51.9); 278 ($M^+ + 1$, 7.7); 279 ($M^+ + 2$, 3.1); 233 ($M^+ -$ ethylene oxide, 100); 158 ($M^+ - OCSCH_3$, 14); 91 (tropylium, 26); 75 (CH_3SCO^+, 13)

[a] Determined from the ^{1}H-NMR spectrum of the crude product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.33, H ±0.27, N ±0.49, Cl ±0.46, S ±0.50.
[d] Recorded on a Perkin-Elmer 781 IR spectrophotometer using a KBr matrix for **3a–d** and a thin film between NaCl windows for **3e–g**.
[e] Recorded on a Varian MAT 711 spectrometer with electron impact source (70 eV).
[f] Reaction crudes were purified by flash chromatography on silica gel using light petroleum ether (bp 60–80°C) EtOAc (65 : 35) as eluent.

Table 2. NMR Data of 2-Methylthio-1,3-oxazoles **3**

	^{1}H-NMR[a] ($CDCl_3$/TMS; 27°C), δ				^{13}C-NMR[b] ($CDCl_3$/TMS; 27°C), δ								
Compound	SCH_3 (s)	CH_3 (t)	CH_2O (q)	miscellaneous	CH_3	SCH_3	OCH_2	C-4	C-5	C-2	C=O	C_{arom}	Other
3a	2.73	1.37	4.40	7.13–7.56 (m, $3H_{arom}$)	13.9	14.3	61.1	126.5	156.2	160.0	161.5	127.9; 128.0; 129.8	
3b	2.72	1.37	4.37	2.41 (s, 3H, 4-CH_3); 7.14 (m, $4H_{arom}$)	14.0	14.4	61.0	127.5	156.6	159.6	161.5	123.8; 127.9; 128.8; 140.2	21.2 (CH_3)
3c	2.72	1.38	4.40	7.38 (d, $2H_{arom}$); 7.96 (d, $2H_{arom}$)	13.9	14.3	61.2	129.1	155.0	160.2	161.4	124.9; 128.2; 129.1; 135.7	
3d	2.73	1.39	4.42	7.37 (m, $2H_{arom}$); 7.94 (m, $2H_{arom}$)	14.0	14.4	61.4	128.8[c]	154.6	160.8	161.4	126.0; 127.9; 128.3[c]; 129.4; 134.2	
3e	2.65	1.37	4.35	2.57 (s, 3H, CH_3)	11.6	14.1	60.4	128.4	156.8	159.1	161.5		13.9 (CH_3)
3f	2.63	1.37	4.33	1.00 (s, 9H, $(CH_3)_3C$); 2.90 (s, 2H, CH_2)	13.8	14.0	60.2	129.5	158.9	159.3	161.3		29.0 ($\underline{C}H_3)_3C$; 32.2 ($(CH_3)_3\underline{C}$; 38.6 (CH_2)
3g	2.57	1.37	4.37	4.30 (s, 2H, $PhCH_2$); 7.20 (s, 5H, Ph)	13.8	14.1	60.5	128.3	158.2	160.0	161.2	126.5; 128.2; 135.6	31.6 (CH_2)

[a] Recorded on a Varian T60-A spectrometer (60 MHz).
[b] Recorded on a Varian FT-80A spectrometer (20 MHz for ^{13}C).
[c] Interchangeable signals.

Table 3. *S*-Phenyl Thiocarboxylates **2** Prepared as Precursors of 1,3-Oxazoles **3**

Product	Yield[a] (%)	mp (°C) found[b]	mp (°C) Lit.	IR (KBr)[c] ν(cm^{-1})	^{1}H-NMR[d] ($CDCl_3$/TMS; 27°C), δ
2a	85	53–54	56[22]	1660, 895	2.37 (s, 3H, CH_3); 7.20–7.60 (m, 8H, H-3, H-4, H-5, SPh)
2b	80	87–88	75[23]	1665, 910	2.37 (s, 3H, CH_3); 7.00–7.63 (m, 7H, H-3, H-5, SPh)
2c	95	80–81	81.5–83[24], 82–84[25]	1670, 910	7.10–7.60 (m, 7H, H-3, H-5, SPh); 7.73–8.17 (m, 2H, H-2, H-6)
2d	83	40–41		1665, 920	7.18–7.58 (m, 7H, H-4, H-5, SPh); 7.77–7.93 (m, 2H, H-2, H-6)
2e	77	yellow oil		1710, 950	2.40 (s, 3H, CH_3); 7.35 (s, 5H, SPh)
2f	66	colorless oil		1700, 1000	1.03 (s, 9H, $(CH_3)_3C$); 2.50 (s, 2H, CH_2); 7.30 (s, 5H, SPh)
2g	81	31–32	34–35[26]	1690, 1000	3.85 (s, 2H, CH_2); 7.23 (s, 5H, Ph); 7.27 (s, 5H, SPh)

[a] Yield of isolated product **2** based on initial acyl chloride or alkanoic acid.
[b] Uncorrected.
[c] Recorded on a Perkin-Elmer 781 IR spectrophotometer.
[d] Recorded on a Varian T60-A spectrometer (60 MHz).

S-Phenyl Thiocarboxylates 2a–g:
2a–d are prepared by the Dalgliesh's method,[15] whereas the procedure reported by Staab[16] is used for the synthesis of *S*-phenyl alkanethioates **2e–g**. Most of these compounds have been described previously but not their spectroscopic parameters (Table 3).

5-Alkyl- and 5-Aryl-4-ethoxycarbonyl-2-methylthio-1,3-oxazoles 3; General Procedure:
In a dried, nitrogen-filled round-bottomed flask fitted with a magnetic stirrer and a rubber septum, KOBu-*t* (1.12 g, 10 mmol) is dissolved in THF (50 mL), and the reaction flask is cooled at −78 °C. A solution of dimethyl *N*-(ethoxycarbonylmethyl)iminodithiocarbonate (1.00 g, 5 mmol)[18,19] in THF (10 mL) is then added dropwise, and stirring is continued at −78 °C for 0.5 h. *S*-Phenyl thiocarboxylate (**2a–g**; 6 mmol) in THF (10 mL) is then added dropwise, and the temperature is allowed to reach 25 °C. The solution is stirred at r.t. for 2 h and quenched with a minimum amount of water to get again a homogeneous solution. Et_2O (50 mL) is then added, and the organic phase is separated, washed with water (2 × 25 mL), and dried ($MgSO_4$). The solvent is evaporated, and the crude product **3** is recrystallized or flash chromatographed on silica gel column (15 cm × 4 cm) using the conditions given in Table 1.

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