A convenient route to 3-substituted isothiazoles using nitrile sulfide cycloaddition chemistry

John Crosby, Marion C. McKie, R. Michael Paton,* and John F. Ross

Department of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh, EH9 3JJ, UK
E-mail: R.M.Paton@ed.ac.uk

Dedicated to Otto Meth-Cohn on the Occasion of his 65th birthday

(received 15 Jun 00; accepted 03 Oct 00; published on the web 11 Oct 00)

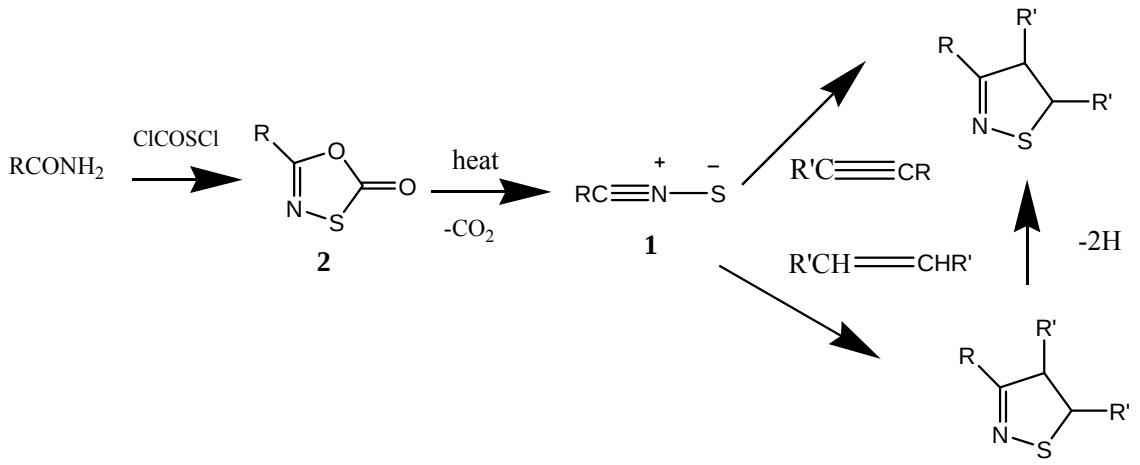
Abstract

Isothiazole-3- and 4-carboxylate esters are readily prepared by 1,3-dipolar cycloaddition of nitrile sulfides, generated by thermal decarboxylation of the corresponding 1,3,4-oxathiazol-2-ones, to acrylate, fumarate and maleate esters, followed by phase-transfer-mediated hypochlorite oxidation of the resulting 2-isothiazoline cycloadducts.

Keywords: Isothiazoles, nitrile sulfide, 1,3-dipolar cycloaddition, hypochlorite oxidation.

Introduction

Isothiazoles show a wide spectrum of biological activity[1] and there is therefore interest in effective methods for their synthesis. One route that has been used[2,3] with some success involves the 1,3-dipolar cycloaddition of nitrile sulfides 1[4] to alkynes. Nitrile sulfides can be generated by thermal decarboxylation of the corresponding 1,3,4-oxathiazol-2-one 2, which are readily prepared from carboxamides (Scheme 1). The range of suitable alkynes, however, is limited by low reactivity and, in some cases, by thermal instability. We have investigated an alternative nitrile sulfide-based approach involving initial cycloaddition to alkenes, which are generally more accessible and of greater reactivity, followed by oxidation of the resulting 2-isothiazoline cycloadducts (Scheme 1).

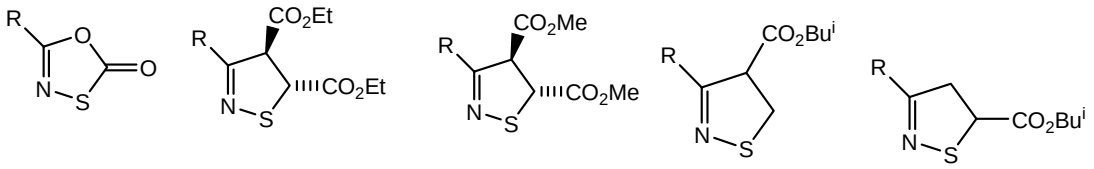


Scheme 1

Results and Discussion

Cycloaddition of Nitrile Sulfides to Alkenes.

Nitrile sulfides are short-lived species prone to fragmentation to sulfur and the corresponding nitrile, and it is therefore necessary for them to be generated *in situ* in the presence of the dipolarophile.[4] In a typical experiment a solution of phenyloxathiazolone 2a in xylene was heated under reflux (~138 °C) with ten equivalents of diethyl fumarate until HPLC analysis showed that all the starting material had been consumed (4.5 h). Removal of the solvent and excess dipolarophile afforded an oil from which 2-isothiazoline 3a (70%) was isolated by crystallisation. The *trans* arrangement of the ethoxycarbonyl groups in the product was evident from the 4 Hz coupling between 4-H and 5-H in the ^{1}H NMR spectrum, which is comparable to those reported for the dimethyl fumarate adduct 4a[5] and the corresponding 2-isoxazoline derived from reaction of diethyl fumarate with benzonitrile oxide (PhC^{o}N^{+}-O^{-}).[6] The structure of adduct 3a was confirmed by X-ray crystallography.[7] 4-Methoxy-, 4-methyl-, and 4-chloro-benzonitrile sulfides 1b-d, and alkanonitrile sulfides 1e-g reacted similarly (Table 1, entries 2-7). A noteworthy feature of these results is the differing times required for the reaction to go to completion; electron-withdrawing substituents decrease the rate of reaction, while electron-donation has the opposite effect in the order Me > Pr > heptyl > 4-MeOC$_6$H$_4$ > 4-MeC$_6$H$_4$ > Ph >> 4-ClC$_6$H$_4$. This effect can be attributed[2a] to the development of a partial positive charge at the 5-position of the oxathiazolone ring in the transition state for the decarboxylation



[1-4, 7, 8: R = a, Ph; b, 4-$MeOC_6H_4$; c, 4-MeC_6H_4; d, 4-ClC_6H_4; e, Me; f, Pr; g, $CH_3(CH_2)_6$]

Table 1. Cycloaddition reactions of nitrile sulfides ($RC^{o}N^{+}$-S^{-}) to alkenes at 135-140 °C

Entry	R	alkene[a]	reactant ratio	reaction time/h	2-isothiazoline(s)			nitrile
						yield/%	ratio[b,c]	yield/%
1	C_6H_5	DEF	1:10	4.5	3a	70	-	d
2	4-$MeOC_6H_4$	DEF	1:10	2.5	3b	80	-	d
3	4-MeC_6H_4	DEF	1:10	4	3c	40	-	d
4	4-ClC_6H_4	DEF	1:10	9.5	3d	67	-	d
5	Me	DEF	1:10	1.0	3e	68	-	d
6	$CH_3(CH_2)_2$	DEF	1:10	1.25	3f	69	-	d
7	$CH_3(CH_2)_6$	DEF	1:10	1.5	3g	70	-	d
8	C_6H_5	DMF	1:4	12	4b	61	-	d
9	4-$MeOC_6H_4$	DEM	1:10	5	3b	23,32[c]	-	67
10	4-MeC_6H_4	DEM	1:8	14	3c	<5[c]	-	>80[c]
11	4-$MeOC_6H_4$	IBA	1:2	5	7b/8b	36[c]	0.33	58
12	4-$MeOC_6H_4$	IBA	1:3	5	7b/8b	40[c]	0.35	53
13	4-$MeOC_6H_4$	IBA	1:5	5	7b/8b	45[c]	0.36	50
14	4-$MeOC_6H_4$	IBA	1:6	5	7b/8b	48[c]	0.36	46
15	4-$MeOC_6H_4$	IBA	1:7	5	7b/8b	51[c]	0.38	43
16	4-$MeOC_6H_4$	IBA	1:9	5	7b/8b	55[c]	0.37	40
17	4-$MeOC_6H_4$	IBA	1:11	5	7b/8b	59[c]	0.37	37

[a] alkenes: (DEF) diethyl fumarate, (DMF) dimethyl fumarate, (DEM) diethyl maleate, (IBA) isobutyl acrylate

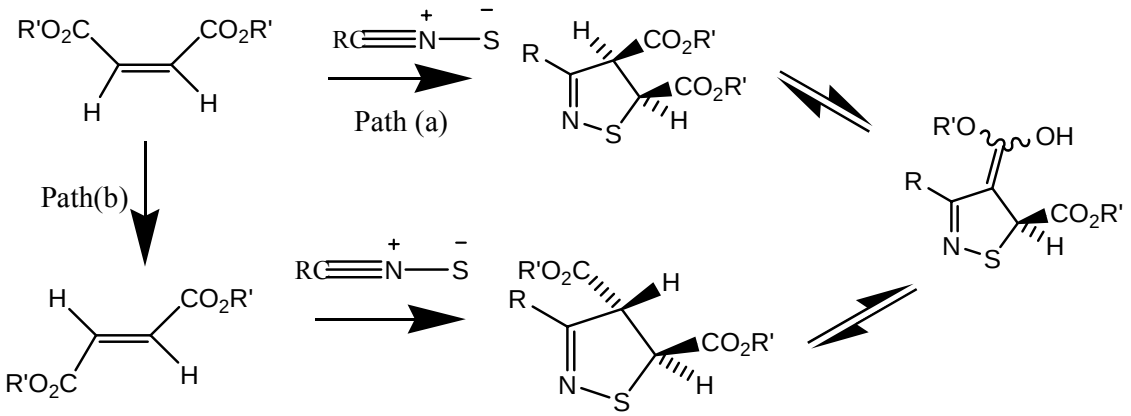
[b] 4-carboxylate (7b) : 5-carboxylate (8b)

[c] determined by HPLC analysis

[d] not determined

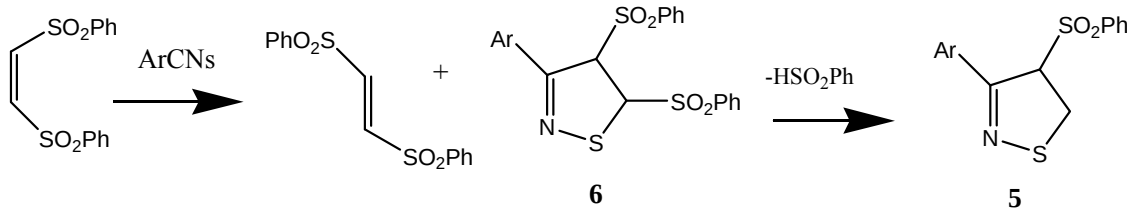
Having established that diethyl fumarate (DEF) is an efficient dipolarophile for trapping a range of nitrile sulfides, the corresponding reaction with diethyl maleate (DEM) was

examined. 4-Methoxy-phenyloxathiazolone 2b and excess DEM (1:10) in xylene were heated under reflux for 5 hours. The only products detected (HPLC) and isolated were the *trans*-isothiazoline 3b (32%) and 4-methoxybenzonitrile (67%). The cycloadduct was identified from its mp (and mixed mp) and its spectroscopic properties by comparison with those of the authentic compound prepared from DEF. Formation of nitriles as by-products is a common feature of nitrile sulfide reactions, particularly with less reactive dipolarophiles, and is attributed to fragmentation of the nitrile sulfide competing with cycloaddition.[4] Similar results were obtained for the reaction of DEM with nitrile sulfide 1c. The low adduct yields are consistent with the reported[8] lower reactivity of *cis*-alkenes. Two possibilities are considered for the formation of the *trans* adduct (Scheme 2): either the nitrile sulfide reacts with the *cis*-alkene and the resulting *cis* adduct rearranges to the thermodynamically more stable *trans* product, possibly *via* enolisation of the 4-carboxy group (path a); or the dipolarophile undergoes *cis* to *trans* isomerisation under the reaction conditions prior to cycloaddition (path b). There is precedent for the former explanation in the work of Rahman and Clapp[6] who observed that, in the corresponding reaction of benzonitrile oxide with DEM, the expected *cis* adduct formed at room temperature rapidly rearranged to the *trans* isomer at 80 °C. On the other hand, examination of the unreacted dipolarophile recovered from the reaction mixture by ^{1}H NMR spectroscopy showed the presence of DEF ($\delta_{=CH}$ 6.4 ppm, *cf* 6.0 ppm for DEM), consistent with path (b). As DEM is thermally stable at the reaction temperature it is assumed that it results, either (i) from a reversible cycloaddition which allows the more stable *trans*-alkene to be generated in the reverse step, similar to that proposed[9] to explain DEF formation in the reaction of arylchlorocarbenes with DEM, or (ii) *via* an isomerisation process induced by a reactive sulfur species formed as a by-product on decomposition of the nitrile sulfide.



Scheme 2

Cis-trans dipolarophile isomerisation was also observed during the reaction of nitrile sulfide 2c with *cis*-1,2-bis(phenylsulfonyl)ethene (*cis*-PSE). Thermolysis of oxathiazolone 2c and *cis*-PSE (1:2.5) in refluxing xylene for 20h afforded the 4-(phenylsulfonyl)isothiazole 5 (38%), rather than the expected isothiazoline 6 (Scheme 3). Presumably the initially formed isothiazoline undergoes spontaneous elimination of phenylsulfonic acid under the reaction conditions. 4-Methylbenzonitrile and sulfur were formed as by-products. The regiochemistry of the adduct was established from its ^{1}H NMR spectrum, which showed a signal at 9.5 ppm characteristic for 5-H of isothiazoles. The excess dipolarophile was recovered and shown from its NMR spectra and mp to have undergone complete conversion to the *trans* isomer (*trans*-PSE). *cis*-PSE was shown to be thermally stable at the reaction temperature (135 °C).



Scheme 3. (Ar = 4-MeC_6H_4).

In order to help distinguish between the two isomerisation pathways (i,ii) a pair of olefinic dipolarophiles (*cis*-, *trans*-stilbene) were selected which were expected to be too unreactive to undergo cycloaddition with nitrile sulfides. Thermolysis of oxathiazolone 2c in the presence of a two-fold excess of *trans*-stilbene gave only sulfur (95%) and 4-methylbenzonitrile (92%) together with recovered *trans*-stilbene (90%); no adduct could be detected by mass spectrometry. However, when *cis*-stilbene was used under similar conditions, sulfur (94%) and 4-methylbenzonitrile (90%) were isolated together with *trans*-stilbene (95%). These results are consistent with pathway (ii) involving oxathiazolone decomposition product(s), presumably sulfur, inducing the *cis* to *trans* rearrangement. This hypothesis is supported by the observation that heating DEM with sulfur at ~220 °C resulted in complete conversion to DEF. The nature of the active species is uncertain, but may be reactive form of sulfur, *eg* S_2 or S_6, resulting from the decomposition of the nitrile sulfide.[10]

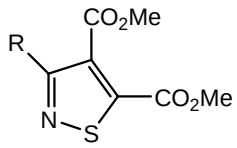
The reaction of 4-methoxybenzonitrile sulfide 1b with isobutyl acrylate afforded 4-methoxybenzonitrile and a regioisomeric mixture of isothiazoline-4- and 5-carboxylate

esters 7b and 8b. The cycloadduct to nitrile product ratio was found to be sensitive to the excess of dipolarophile used, varying form 0.62 for dipolarophile:dipole = 2:1 to 1.60 at 11:1 (Table 1, entries 10-17). The regioisomer ratio (~0.35) remained constant within experimental error. The individual regioisomers were readily identified from their NMR spectra; *eg* the 4-carboxylate 7b showed characteristic ^{13}C peaks for *C*H-4 and *C*H_2-5 at 56.9 and 37.4 ppm respectively, whereas order was reversed for the 5-carboxylate isomer 8b [δ_C 41.0 (*C*H_2-4), 48.8 (*C*H-5)]. The modest regioselectivity observed for these nitrile sulfide / acrylate ester cycloadditions (25:75) differs markedly from that reported[8] for the corresponding reactions of nitrile oxides, which are much more selective, typically giving isomer ratios of *ca* 5:95. The lower selectivity in the nitrile sulfide case can be attributed to greater dipole-HOMO control in the cycloaddition.[2c]

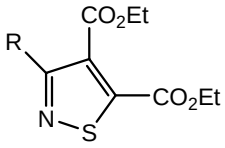
Oxidation of 2-isothiazolines to isothiazoles

Previous work by Howe and Franz[5] showed that isothiazoline 4a could be dehydrogenated to isothiazole 9a in moderate yield (40%) using excess DDQ in refluxing chlorobenzene (5h at ~130 °C). In order to avoid these forcing conditions and facilitate isolation of the product, we have explored the feasibility of using aqueous sodium hypochlorite in a two-phase reaction. In a pilot experiment a solution of isothiazoline 4a in dichloromethane was stirred vigorously with 8% aq. NaOCl at room temperature. TLC and HPLC analysis showed that after 3 weeks 4a had been transformed into 9a, which was isolated in 92% yield (99% by HPLC). Isothiazoline 3b was converted to isothiazole 10b (93%) similarly (Table 2, entries 1 & 2).

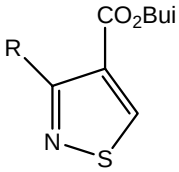
Although these results showed that hypochlorite is an effective oxidising agent, the reaction times were unacceptably long. In order to accelerate the process benzyltriethylammonium chloride was added as a phase transfer catalyst. By this means the reaction times were greatly reduced; *eg* isothiazoline 3a was converted to isothiazole 10a within 5 hours and in high yield (92%) (Table 2, entry 3). To illustrate the general utility of the method a series of oxidations were carried out using selected 3-aryl- and 3-alkyl-isothiazoledicarboxylates, and isothiazole-4-, and –5-carboxylates 7b and 8b (entries 4-9). In all cases the reactions were complete in 5 hours or less, and the yields were good (>80%). Attempted dehydrogenation of isothiazoline 4a using oxygen at room temperature, by thermolysis (164 °C), and thermolysis in the presence of air or sulfur gave low conversions to isothiazole 9a (entries 10-13). However, when a combination of air or oxygen with sulfur was used moderate yields (20%, 44%) of the isothiazole were achieved (entries 14,15).



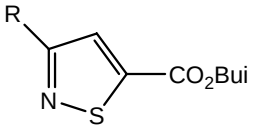
9



10



11



12

[9-12: R = a, Ph; b, 4-$MeOC_6H_4$; c, 4-MeC_6H_4; d, 4-ClC_6H_4; e, Me; f, Pr; g, $CH_3(CH_2)_6$]

Table 2. Oxidation of 2-isothiazolines to isothiazoles

Entry	2-isothiazoline	reaction conditions			isothiazole		unreacted
		reagent[a]	time	temp./°C		yield/%	isothiazoline
1	4a	NaOCl	21d	~ 18	9a	92,99[c]	*b*
2	3b	NaOCl	21d	~ 18	10b	93	*b*
3	3a	NaOCl + cat.	5h	~ 18	10a	92	*b*
4	3d	NaOCl + cat.	5h	~ 18	10d	94	*b*
5	3e	NaOCl + cat.	5h	~ 18	10e	85	*b*
6	3f	NaOCl + cat.	5h	~ 18	10f	81	*b*
7	3g	NaOCl + cat.	5h	~ 18	10g	80	*b*
8	7b	NaOCl + cat.	4.5 h	~ 18	11b	80	*b*
9	8b	NaOCl + cat.	4h	~ 18	12b	86	*b*
10	4a	O_2	26 h	~ 18	9a	< 1	100
11	4a	N_2	24 h	164[d]	9a	2[c]	98[c]
12	4a	air	24 h	164[d]	9a	4[c]	95[c]
13	4a	$N_2 + S_8$	24 h	164[d]	9a	3[c]	97[c]
14	4a	air + S_8	48 h	164[d]	9a	20[c]	79[c]
15	4a	$O_2 + S_8$	48 h	164[d]	9a	44[c]	52[c]

[a] 8 % aq. NaOCl, cat. $BnN^+Et_3.Cl^-$

[b] not detected

[c] determined by HPLC analysis

[d] in mesitylene under reflux

In conclusion, for ease of work-up and high product yields phase-transfer mediated hypochlorite oxidation at room-temperature of 2-isothiazolines to isothiazoles is more effective than dehydrogenation with DDQ. The two-step route to isothiazoles involving

nitrile sulfide cycloaddition to electron-deficient alkenes, followed by oxidation of the resulting isothiazoline cycloadduct thus affords isothiazoles in 55-80% overall yield.

Experimental Section

General Procedures. The instrumentation for recording IR, ^{1}H and ^{13}C NMR, and mass spectra, and the analytical methods used for monitoring the reactions were as previously described.[11,12] Oxathiazolones 2a-2f[3] and dimethyl 3-phenylisothiazole-4,5-dicarboxylate (9a)[2a] were prepared as previously reported. NMR spectra were recorded in $CDCl_3$ unless otherwise stated.

5-Heptyl-1,3,4-oxathiazol-2-one (2g). This compound was prepared (61%) from octanamide and chlorocarbonylsulfenyl chloride as previously described[3] for the propyl analogue 2f. Bp 94 °C at 1.0 mmHg (Found: C, 53.9; H, 7.7; N, 7.1. $C_9H_{15}NO_2S$ requires C, 53.7; H, 7.5; N, 7.0%); ν_{max} (film) 1765 cm^{-1} (C=O).

Reaction of nitrile sulfides with dialkyl fumarates. The general procedure was to heat under reflux (~138 °C) a solution of the 1,3,4-oxathiazol-2-one (2) (24 mmol) and the alkene (240 mmol) in dry xylene. The reaction was continued until HPLC analysis showed that all the starting material had been consumed. After evaporation under reduced pressure to remove the solvent and excess dipolarophile, the dialkyl (*E*)-2-isothiazoline-4,5-dicarboxylatewas separated from nitrile and sulfur by-products by distillation and/or recrystallisation. Reaction conditions and product yields are given in Table 1.

Diethyl (*E*)-3-phenyl-2-isothiazoline-4,5-dicarboxylate (3a). Mp 62-63 °C (from EtOH) (Found: C, 58.4; H, 5.6; N, 4.5. $C_{15}H_{17}NO_4S$ requires C, 58.6; H, 5.6; N, 4.6%); ν_{max} (Nujol) 1732 cm^{-1} (C=O); δ_H 7.88-7.56 (m, 2H, PhH), 7.42-7.24 (m, 3H, PhH), 5.17 (d, 1H, *J* = 4 Hz, 5-H), 4.76 (d, 1H, *J* = 4 Hz, 4-H), 4.17 (q, 2H, OCH_2), 4.10 (q, 2H, OCH_2), 1.24 (t, 3H, CH_3), 1.07 (t, 3H, CH_3); δ_C 170.4, 168.5 (C=O), 161.7 (C-3), 133.1 (PhC), 130.2, 128.4, 127.9 (5 PhCH), 62.3, 62.1 (OCH_2), 59.3 (C-5), 53.6 (C-4), 14.0, 13.8 (CH_3); *m/z* 307 (M^+), 188, 135 ($PhCNS^+$), 103 ($PhCN^+$).

Diethyl (*E*)-3-(4-methoxyphenyl)-2-isothiazoline-4,5-dicarboxylate (3b). Mp 45-46 °C (from EtOH) (Found: C, 57.1; H, 5.7; N, 4.0. $C_{16}H_{19}NO_5S$ requires C, 57.0; H, 5.8; N, 4.1%); ν_{max} (Nujol) 1731 cm^{-1} (C=O); δ_H 7.70 (d, 2H, *J* = 9 Hz, ArH), 6.83 (d, 2H, *J* = 9 Hz, ArH), 5.08 (d, 1H, *J* = 4 Hz, 5-H), 4.71 (d, 1H, *J* = 4 Hz, 4-H), 4.18 (q, 2H, OCH_2), 4.10 (q, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 1.24 (t, 3H, CH_3), 1.07 (t, 3H,

CH_3); δ_C 170.5, 168.7 (C=O), 161.4 (C-3), 161.2, 126.2 (ArC), 129.6, 113.8 (4 ArCH), 62.3, 62.1 (OCH_2), 59.4 (C-5), 55.3 (OCH_3), 53.5 (C-4), 14.0, 13.9 (CH_3); *m/z* 337 (M^+), 218, 165 ($ArCNS^+$), 133 ($ArCN^+$).

Diethyl (*E*)-3-(4-methylphenyl)-2-isothiazoline-4,5-dicarboxylate (3c). Oil (Found: M^+, 321.1034. $C_{16}H_{19}NO_4S$ requires M 321.10347); ν_{max} (Nujol) 1735 cm^{-1} (C=O); δ_H 7.7 (d, 2H, ArH), 7.1 (d, 2H, ArH), 5.1 (d, 1H, *J* = 4 Hz, 5-H), 4.8 (d, 1H, *J* = 4 Hz, 4-H), 4.2 (q, 4H, OCH_2), 2.3 (s, 3H, CH_3), 1.2 (t, 6H, CH_3); δ_C 170.0, 168.2 (C=O), 161.5 (C-3), 140.0, 130.2 (ArC), 128.7, 127.5 (4 ArCH), 61.8, 61.6 (OCH_2), 59.1 (C-5), 53.2 (C-4), 20.9 (CH_3), 13.4 (2 CH_3); *m/z* 321 (M^+).

Diethyl (*E*)-3-(4-chlorophenyl)-2-isothiazoline-4,5-dicarboxylate (3d). Mp 49-50 °C (from EtOH) (Found: C, 52.9; H, 4.7; N, 4.0. $C_{15}H_{16}ClNO_4S$ requires C, 52.7; H, 4.7; N, 4.1%); ν_{max} (Nujol) 1733 cm^{-1} (C=O); δ_H 7.68 (d, 2H, *J* = 8.5 Hz, ArH), 7.30 (d, 2H, *J* = 8.5 Hz, ArH), 5.10 (d, 1H, *J* = 4 Hz, 5-H), 4.76 (d, 1H, *J* = 4 Hz, 4-H), 4.22 (q, 2H, OCH_2), 4.10 (q, 2H, OCH_2), 1.25 (t, 3H, CH_3), 1.08 (t, 3H, CH_3); δ_C 170.3, 168.3 (C=O), 160.6 (C-3), 136.2, 131.5 (ArC), 129.2, 128.7 (4 ArCH), 62.4, 62.3 (OCH_2), 59.1 (C-5), 53.6 (C-4), 14.0, 13.9 (CH_3); *m/z* 343 & 341 (M^+), 224 & 222, 196 & 198 ($ArCNS^+$), 171 & 169 ($ArCN^+$).

Diethyl (*E*)-3-methyl-2-isothiazoline-4,5-dicarboxylate (3e). Bp 95 °C at 0.015 mmHg (Found: C, 49.1; H, 6.2; N, 5.8. $C_{10}H_{15}NO_4S$ requires C, 49.0; H, 6.2; N, 5.7%); ν_{max} (Nujol) 1730 cm^{-1} (C=O); δ_H 4.83 (d, 1H, *J* = 6 Hz, 5-H), 4.53 (d, 1H, *J* = 6 Hz, 4-H), 4.22 (q, 2H, OCH_2), 4.17 (q, 2H, OCH_2), 2.15 (s, 3H, CH_3), 1.80 (t, 3H, CH_3), 1.40 (t, 3H, CH_3); δ_C 170.6, 167.9 (C=O), 162.3 (C-3), 63.4 (C-5), 62.2 (2 OCH_2), 52.0 (C-4), 20.0 (CH_3), 14.1 (2 CH_3); *m/z* 245 (M^+), 126, 73 ($MeCNS^+$).

Diethyl (*E*)-3-propyl-2-isothiazoline-4,5-dicarboxylate (3f). Bp 107 °C at 0.015 mmHg (Found: C, 52.8; H, 7.0; N, 5.1. $C_{12}H_{19}NO_4S$ requires C, 52.7; H, 7.0; N, 5.1%); ν_{max} (Nujol) 1735 cm^{-1} (C=O); δ_H 4.79 (d, 1H, *J* = 5 Hz, 5-H), 4.50 (d, 1H, *J* = 5 Hz, 4-H), 4.21 (q, 2H, OCH_2), 4.16 (q, 2H, OCH_2), 2.45 (t, 2H, $CH_2CH_2CH_3$), 1.90-1.48 (m, 2H, $CH_2CH_2CH_3$), 1.28 (t, 3H, CH_3), 1.24 (t, 3H, CH_3), 0.92 (t, 3H, CH_3); δ_C 170.7, 168.0 (C=O), 166.1 (C-3), 62.3 (C-5), 62.2 (2 OCH_2), 51.9 (C-4), 35.6, 19.8 (CH_2), 14.1 (CH_3), 13.7 (2 CH_3); *m/z* 273 (M^+).

Diethyl (*E*)-3-heptyl-2-isothiazoline-4,5-dicarboxylate (3g). Bp 170 °C at 0.05 mmHg (Found: C, 58.2; H, 8.0; N, 4.3. $C_{16}H_{27}NO_4S$ requires C, 58.3; H, 8.3; N, 4.3%); ν_{max} (Nujol) 1735 cm^{-1} (C=O); δ_H 4.80 (d, 1H, *J* = 5 Hz, 5-H), 4.55 (d, 1H, *J* = 5 Hz, 4-H), 4.22 (q, 2H, OCH_2), 4.17 (q, 2H, OCH_2), 2.48 (t, 2H, $CH_2(CH_2)_5CH_3$), 1.88-1.26 (m, 16H, $CH_2(CH_2)_5CH_3$ & 2 CH_3), 0.86 (t, 3H, CH_3); δ_C 170.2, 167.6 (C=O), 165.8 (C-

3), 61.9 (C-5), 61.7 (2 OCH_2), 51.5 (C-4), 33.3, 31.3, 28.7, 28.6, 26.0, 22.2 (CH_2), 13.7 (3 CH_3); *m/z* 329 (M^+).

Dimethyl (*E*)-3-phenyl-2-isothiazoline-4,5-dicarboxylate (4a). Mp 59-60 °C (from EtOH) lit.[5] a viscous oil of mp ~ 6°C) (Found: C, 55.7; H, 4.5; N, 4.8. $C_{13}H_{13}NO_4S$ requires C, 55.9; H, 4.7; N, 5.0%); ν_{max} (Nujol) 1736 cm^{-1} (C=O); *m/z* 279 (M^+), 188, 135 ($PhCNS^+$), 103 ($PhCN^+$).

Reaction of 4-methoxybenzonitrile sulfide (1b) with isobutyl acrylate. A solution of 5-(4-methoxyphenyl)-1,3,4-oxathiazol-2-one (2b) (4.0 g, 19 mmol) and isobutyl acrylate (7.6 g, 59 mmol) in dry xylene (100 ml) was heated under reflux in a nitrogen atmosphere until HPLC analysis showed that no oxathiazolone remained (5 h). The mixture was concentrated under vacuum to a yellow oil, which was suspended in cold ethanol to give white needles of 4-methoxybenzonitrile (0.78, 31%), mp 59 °C, ν_{max} (Nujol) 2210 cm^{-1} (CºN), *m/z* 133 (M^+). Chromatography of the residue (silica / heaxane-Et_2O, 1:1) afforded the following compounds in order of elution.

Isobutyl 3-(4-methoxyphenyl)-2-isothiazoline-5-carboxylate (8b) (1.17 g, 21%) as white crystals. Mp 51-52 °C (from ethanol) (Found: C, 61.5; H, 6.5; N, 4.7. $C_{15}H_{19}NO_3S$ requires C, 61.4; H, 6.5; N, 4.8%); ν_{max} (Nujol) 1733 cm^{-1} (C=O); δ_H 7.66 (d, 2H, *J* = 9 Hz, ArH), 6.85 (d, 2H, *J* = 9 Hz, ArH), 4.54 (dd, 1H, $J_{5,4b}$ = 11 Hz, $J_{5,4a}$ = 5 Hz, 5-H), 3.99 (dd, 1H, $J_{4a,4b}$ = 17 Hz, 4b-H), 3.94 (d, 2H, OCH_2), 3.78 (s, 3H, OCH_3), 3.46 (dd, 1H, 4a-H), 1.95 (m, 1H, CH), 0.90 (d, 6H, CH_3); δ_C 171.5 (C=O), 161.6 (C-3), 160.9, 126.2 (ArC), 128.8, 113.7 (4 ArCH), 71.6 (OCH_2), 55.2 (OCH_3), 48.8 (C-5), 41.0 (C-4), 27.5 (CH), 18.8 (2 CH_3); *m/z* 293 (M^+), 165 ($ArCNS^+$), 133 ($ArCN^+$).

Isobutyl 3-(4-methoxyphenyl)-2-isothiazoline-4-carboxylate (7b) (0.33 g, 6 %) as white needles. Mp 42-43 °C (from hexane) (Found: C, 61.3; H, 6.5; N, 4.6. $C_{15}H_{19}NO_3S$ requires C, 61.4; H, 6.5; N, 4.8%); ν_{max} (Nujol) 1730 cm^{-1} (C=O); δ_H 7.73 (d, 2H, *J* = 9 Hz, ArH), 6.88 (d, 2H, *J* = 9 Hz, ArH), 4.65 (dd, 1H, $J_{4,5a}$ = 9 Hz, $J_{4,5b}$ = 7 Hz, 4-H), 3.92-3.70 (m, 6H, 5a-H, 5b-H, OCH_2), 3.80 (s, 3H, OCH_3), 1.82 (m, 1H, CH), 0.80 (d, 6H, CH_3); δ_C 169.8 (C=O), 161.8 (C-3), 160.7, 126.3 (ArC), 128.9, 113.6 (4 ArCH), 71.5 (OCH_2), 56.9 (C-4), 55.1 (OCH_3), 37.4 (C-5), 27.3 (CH), 18.6 (2 CH_3); *m/z* 293 (M^+), 165 ($ArCNS^+$), 133 ($ArCN^+$).

Reaction of nitrile sulfides with diethyl maleate

4-Methoxybenzonitrile sulfide (1b).- A suspension of 5-(4-methoxyphenyl)-1,3,4-oxathiazol-2-one (2b) (2.0 g, 9.6 mmol) and diethyl maleate (16.5 g, 9.6 mmol) in dry xylene (150 ml) was heated under reflux in a nitrogen atmosphere until HPLC analysis showed that no oxathiazolone remained (5 h). The mixture was concentrated under

vacuum to a brown oil which was chromatographed on silica. Elution with CH_2Cl_2 yielded a yellow oil which solidified on treatment with cold ethanol to give a white crystalline solid, which was identified as diethyl (*E*)-3-(4-methoxyphenyl)-2-isothiazoline-4,5-dicarboxylate (3b) (23%) by comparison of its physical and spectroscopic properties with those of an authentic sample; mp and mixed mp 45-46 °C. The reaction was repeated in the presence of an internal standard [dimethyl 3-(4-chlorophenyl)isothiazole-4,5-dicarboxylate (9d)] to determine the yield of isothiazoline 3b (32%) and 4-methoxybenzonitrile (67%) by HPLC analysis. 4-Methylbenzonitrile sulfide (1c).- The corresponding reaction of 5-(4-methylphenyl)-1,3,4-oxathiazol-2-one (2c) and diethyl maleate afforded a brown oil which was shown by HLPC analysis to contain 4-methylbenzonitrile (80%) together with traces (<5%) of diethyl (*E*)-3-(4-methylphenyl)-2-isothiazoline-4,5-dicarboxylate (3c). ^{1}H NMR of recovered dipolarophile: δ_H 6.0 (s, 2H, CH=), 3.8 (q, 4H, OCH_2), 0.9 (t, 6H, CH_3), indistinguishable from that of authentic diethyl fumarate. A sample of diethyl maleate [δ_H 6.4 (s, 2H, CH=), 3.8 (q, 4H, OCH_2), 0.9 (t, 6H, CH_3)] was recovered unchanged after heating for 1 h under reflux (~225 °C) in an atmosphere of nitrogen. A repeat experiment in the presence of sulfur afforded only diethyl fumarate.

Reaction of 4-methylbenzonitrile sulfide (1c) with (*Z*)-1,2-bis(phenylsulfonyl)ethene. A suspension of 5-(4-methylphenyl)-1,3,4-oxathiazol-2-one (2c) (685 mg, 3.5 mmol) and (*Z*)-1,2-bis(phenylsulfonyl)-ethene (3.0 g, 9.7 mmol) in dry xylene (40 ml) was heated under reflux in a nitrogen atmosphere for 20 h. Removal of the solvent under vacuum gave a dark brown solid which was extracted with CH_2Cl_2. The solid residue (1.42 g) was identified as (*E*)-1,2-bis(phenylsulfonyl)ethene, mp 211 °C (lit.[13] 223 °C); δ_H 8.0-7.5 (m, 10H, PhH), 7.4 (s, 2H, CH=); δ_C 140.4 (CH=), 139.6 (PhC), 134.8, 129.7, 128.4 (5 PhCH). Chromatography of the filtrate (silica / hexane-CH_2Cl_2 1:1) afforded in order of elution: sulfur (0.09 g), 4-methylbenzonitrile (0.59 g), (*E*)-1,2-bis(phenylsulfonyl)ethene (0.25 g), and 4-(phenylsulfonyl)-3-(4-methylphenyl)isothiazole (5) (0.42 g, 38%) (Found: M^+, 315.0383. $C_{16}H_{13}NO_2S_2$ requires M 315.03877); ν_{max} (Nujol) 1340, 1120 cm^{-1} (SO_2); δ_H 9.45 (s, 1H, 5-H), 8.4-7.4 (m, 9H, ArH), 2.3 (s, 3H, CH_3); δ_C 156.2 (C-3), 139.1 (C-4), 139.9, 130.3 (ArC), 132.7, 128.9, 128.3, 128.0, 127.3, 127.9 (9 ArCH), 20.6 (CH_3); *m/z* 315 (M^+). A sample of (*Z*)-1,2-bis(phenylsulfonyl)ethene was recovered unchanged after heating for 20h in xylene under reflux in an atmosphere of nitrogen.

Thermolysis of 5-(4-methylphenyl)-1,3,4-oxathiazol-2-one (2c) with (*E*) and (*Z*)-stilbenes.

(*E*)-stilbene.- A suspension of oxathiazolone 2c (750 mg, 3.9 mmol) and (*E*)-stilbene (1.425 g, 7.9 mmol) in xylene (35 ml) was heated under reflux for 17.5 h. From the reaction mixture were isolated by crystallisation and chromatography: (*E*)-stilbene (90%, mp and mixed mp 121-122 °C, lit.[14] 122-124 °C), sulfur (95%) and 4-methylbenzonitrile (92%). (*Z*)-stilbene.- A solution of oxathiazolone 2c (1.44 g, 7.5 mmol) and (*Z*)-stilbene (2 ml, 11.2 mmol) in xylene (40 ml) was heated under reflux for 7 h. From the reaction mixture were isolated by crystallisation and chromatography: (*E*)-stilbene (95%, mp and mixed mp 121-122 °C), sulfur (95%) and 4-methylbenzonitrile (90%); residual (*Z*)-stilbene was not detected.

General procedure for Oxidation of 2-isothiazolines to isothiazoles using aq. NaOCl. To a solution of the oxathiazolone (1.43 mmol) dissolved in CH_2Cl_2 (30 ml) was added 8% aq. NaOCl (30 ml). The mixture was stirred vigorously until no isothiazoline was detected by TLC or HPLC. The organic layer was separated, washed (water), dried ($MgSO_4$), and concentrated to an oil which was chromatographed on silica. Elution with CH_2Cl_2 yielded the isothiazole which was crystallised form cold ethanol. The reaction conditions and product yields are given in Table 2.

Dimethyl 3-phenylisothiazole-4,5-dicarboxylate (9a). Mp and mixed mp 72-73 °C (lit.[2a] 72-73 °C).

Diethyl 3-(4-methoxyphenyl)isothiazole-4,5-dicarboxylate (10b). Mp 42-43 °C (from EtOH) (Found: C, 57.1; H, 5.2; N, 4.2. $C_{16}H_{17}NO_5S$ requires C, 57.3; H, 5.1; N, 4.2%); ν_{max} (Nujol) 1723 cm^{-1} (C=O); δ_H 7.65 (d, 2H, *J* = 9 Hz, ArH), 6.92 (d, 2H, *J* = 9 Hz, ArH), 4.37 (m, 4H, OCH_2), 3.80 (s, 3H, OCH_3), 1.36 (t, 3H, CH_3), 1.30 (t, 3H, CH_3); *m/z* 335 (M^+), 133 ($ArCN^+$).

General procedure for Oxidation of 2-isothiazolines to isothiazoles using aq NaOCl and a phase-transfer catalyst (benzyltriethylammonium chloride). To a solution of the oxathiazolone (1.4 mmol) dissolved in CH_2Cl_2 (20 ml) was added 8% aq. NaOCl (40 ml) and benzyltriethylammonium chloride (0.2 mmol). The mixture was stirred vigorously until no isothiazoline was detected by HPLC analysis (3 weeks). The organic layer was separated, washed (water), dried ($MgSO_4$), and concentrated under vacuum. Solid products were purified by recrystallisation, and liquids by distillation under reduced pressure. The reaction conditions and product yields are given in Table B.

Diethyl 3-phenylisothiazole-4,5-dicarboxylate (10a). Bp 175 °C at 0.04 mmHg (Found: C, 58.8; H, 4.9; N, 4.8. $C_{15}H_{15}NO_4S$ requires C, 59.0; H, 5.0; N, 4.6%); ν_{max} (Nujol) 1735 cm^{-1} (C=O); δ_H 7.80-7.60 (m, 2H, PhH), 7.50-7.36 (m, 3H, PhH), 4.39 (q, 2H, OCH_2), 4.37 (q, 2H, OCH_2), 1.37 (t, 3H, CH_3), 1.30 (t, 3H, CH_3); *m/z* 335 (M^+), 133 ($ArCN^+$).

Diethyl 3-(4-chlorophenyl)isothiazole-4,5-dicarboxylate (10d). Mp 46-47 °C (from EtOH) (Found: C, 52.7; H, 4.1; N, 4.0. $C_{15}H_{14}ClNO_4S$ requires C, 53.0; H, 4.2; N, 4.1%); ν_{max} (Nujol) 1730 cm^{-1} (C=O); δ_H 7.64 (d, 2H, *J* = 8.5 Hz, ArH), 7.38 (d, 2H, *J* = 8.5 Hz, ArH), 4.39 (q, 2H, OCH_2), 4.37 (q, 2H, OCH_2), 1.36 (t, 3H, CH_3), 1.29 (t, 3H, CH_3); *m/z* 341 & 339 (M^+).

Diethyl 3-methyl-2-isothiazole-4,5-dicarboxylate (10e). Bp 80 °C at 0.01 mmHg (Found: C, 49.3; H, 5.4; N, 5.6. $C_{10}H_{13}NO_4S$ requires C, 49.4; H, 5.4; N, 5.8%); ν_{max} (Nujol) 1725 cm^{-1} (C=O); δ_H 4.37 (q, 2H, OCH_2), 4.35 (q, 2H, OCH_2), 2.52 (s, 3H, CH_3), 1.34 (t, 6H, CH_3); *m/z* 243 (M^+).

Diethyl 3-propyl-2-isothiazole-4,5-dicarboxylate (10f). Bp 120 °C at 0.04 mmHg (Found: C, 53.2; H, 6.3; N, 5.4. $C_{12}H_{17}NO_4S$ requires C, 53.1; H, 6.3; N, 5.2%); ν_{max} (Nujol) 1730 cm^{-1} (C=O); δ_H 4.42 (q, 2H, OCH_2), 4.38 (q, 2H, OCH_2), 2.87 (t, 2H, $CH_2CH_2CH_3$), 1.94-1.56 (m, 2H, $CH_2CH_2CH_3$), 1.38 (t, 6H, CH_3), 0.98 (t, 3H, CH_3); *m/z* 271 (M^+).

Diethyl 3-heptyl-2-isothiazole-4,5-dicarboxylate (10g). Bp 160 °C at 0.04 mmHg (Found: C, 58.7; H, 7.7; N, 4.3. $C_{16}H_{25}NO_4S$ requires C, 58.5; H, 7.7; N, 4.5%); ν_{max} (Nujol) 1725 cm^{-1} (C=O); δ_H 4.42 (q, 2H, OCH_2), 4.38 (q, 2H, OCH_2), 2.90 (t, 2H, $CH_2(CH_2)_5CH_3$), 1.90-1.18 (m, 16H, $CH_2(CH_2)_5CH_3$ & 2 CH_3), 0.89 (t, 3H, CH_3); *m/z* 327 (M^+).

Isobutyl 3-(4-methoxyphenyl)isothiaxole-4-carboxylate (11b). Bp 160 °C at 0.01 mmHg (Found: C, 62.0; H, 5.9; N, 4.9. $C_{15}H_{17}NO_3S$ requires C, 61.8; H, 5.9; N, 4.8%); ν_{max} (Nujol) 3105 (C-H), 1727 cm^{-1} (C=O); δ_H 9.30 (5-H), 7.60 (d, 2H, *J* = 9 Hz, ArH), 6.90 (d, 2H, *J* = 9 Hz, ArH), 4.02 (d, 2H, OCH_2), 3.82 (s, 3H, OCH_3), 1.91 (m, 1H, CH), 0.89 (d, 6H, CH_3); δ_C 168.0 (C=O), 162.0 (C-3), 160.1, 127.3 (ArC), 1555.5 (C-5), 130.2, 113.0 (4 ArCH), 70.9 (OCH), 55.0 (OCH_3), 27.4 (CH), 18.8 (2 CH_3); *m/z* 291 (M^+), 133 ($ArCN^+$).

Isobutyl 3-(4-methoxyphenyl)isothiaxole-5-carboxylate (12b) Mp 82-83 °C (Found: C, 61.5; H, 5.9; N, 4.7. $C_{15}H_{17}NO_3S$ requires C, 61.8; H, 5.9; N, 4.7%); ν_{max} (Nujol) 3310 (C-H), 17 23 cm^{-1} (C=O); δ_H 7.92 (4-H), 7,82 (d, 2H, *J* = 9 Hz, ArH), 6.84 (d, 2H, *J* = 9 Hz, ArH), 4.05 (d, 2H, OCH_2), 3.89 (s, 3H, OCH_3), 2.10 (m, 1H, CH), 1.02 (d, 6H, CH_3); δ_C 167.7 (C=O), 160.8 (C-3), 157.4 (C-5), 160.1, 127.1 (ArC), 128.2, 114.2

(4 ArCH), 71.7 (OCH_2), 55.2 (OCH_3), 27.7 (CH), 18.9 (2 CH_3); *m/z* 291 (M^+), 133 ($ArCN^+$).

Acknowledgements

We are grateful to the EPSRC for research and maintenance (M.C.McK & J.F.R) grants.

References

1. For reviews of isothiazoles see: (a) Pain, D. L.; Peart, B. J.; Wooldridge, K. R. H. *Comprehensive Heterocyclic Chemistry*; **1984**; vol. 6, chapter 4.17. (b) Chapman, R. F.; Peart, B. j. *Comprehensive Heterocyclic Chemistry II*; **1996**; vol. 3, chapter 3.07.
2. Howe, R. K.; Gruner, T. A.; Carter, L. G.; Black, L. L.; Franz, J. E. *J. Org. Chem.* **1978**, 43, 3736. (b) Yoshida, H.; Taketani, H.; Ogata, T.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1976**, 49, 3124. (c) Sanders, M. J.; Dye, S. L.; Miller, A. G.; Grunwell, J. R. *J. Org. Chem.* **1979**, 44, 510. (d) McKie, M. C.; Paton, R. M. *J. Chem. Res.* **1987**, (*S*) 245, (*M*), 2051. (e) Brownsort, P. A.; Paton, R. M. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 2339. (f) Brownsort, P. A.; Paton, R. M.; Sutherland, A. G. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1679 and references therein.
3. Damas, A. M.; Gould, R. O.; Harding, M. M.; Paton, R. M.; Ross, J. F.; Crosby, J. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2991 and references therein.
4. For a review of nitrile sulfide chemistry see Paton, R. M. *Chem. Soc. Rev.* **1989**, 18, 33.
5. Howe, R. H.; Franz, J. E. *J. Org. Chem.* **1978**, 43, 3742.
6. Rahman, Clapp, L. *J. Org. Chem.* **1976**, 41, 122.
7. Gould, R. O.; Paton, R. M.; Ross, J. F. unpublished observations.
8. Caramella, P.; Grünanger, P. In *1,3-Dipolar Cycloaddition Chemistry,* ed.; Padwa, A. Wiley: New York, 1984 chapter 3.
9. Doyle, M. P.; Low, K. L.; Nishioka, L. I.; McVickar, M. B.; Liu, M. T. H. *Tetrahedron Lett.* 1986, 27, 4395.
10. Wentrup, C.; Kambouris, P. *Chem. Rev.* **1991**, 91, 363.
11. Greig, D. J.; McPherson, M.; Paton, R. M.; Crosby, J. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 1205.

12. Blake, A. J.; Boyd, E. C.; Gould, R. O.; Paton, R. M. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 2841.
13. De Lucchi, O.; Lucchini, V.; Pasquato, V.; Modena, G. *J. Org. Chem.* **1984**, 49, 596.
14. *Dictionary of Organic Compounds;* Ed.; Buckingham, J. Chapman & Hall: 1982.

