Tetrahedron 67 (2011) 3348–3354

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Regioselective hydrodehalogenation of 3,5-dihaloisothiazole-4-carbonitriles: synthesis of 3-haloisothiazole-4-carbonitriles

Heraklidia A. Ioannidou, Panayiotis A. Koutentis *

Department of Chemistry, University of Cyprus, PO Box 20537, 1678 Nicosia, Cyprus

ARTICLE INFO

Article history:
Received 1 February 2011
Received in revised form 1 March 2011
Accepted 21 March 2011
Available online 11 April 2011

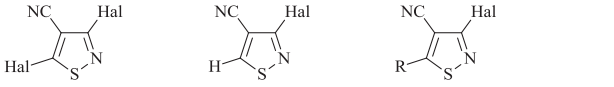
ABSTRACT

3,5-Dibromoisothiazole-4-carbonitrile **1** treated with Zn or In dust (5 equiv) and HCO_2H undergoes regioselective hydrodebromination to give 3-bromoisothiazole-4-carbonitrile **3** in 70–74% yield. Similarly, 5-bromo and iodo 3-chloroisothiazole-4-carbonitriles **8** and **9** give 3-chloroisothiazole-4-carbonitrile **4** in 77 and 85% yields, respectively. Also hydrodeamination of 5-amino-3-chloroisothiazole-4-carbonitrile **7** using isoamyl nitrite gives the latter in 95% yield. The dibromoisothiazole **1** reacts with Zn dust in either DCO_2D or HCO_2D to give 3-bromo-5-deuterioisothiazole-4-carbonitrile **10** in 71 and 58% yields, respectively. The 3-bromoisothiazole **3** reacts with cyclic dialkylamines to give the corresponding 2-(dialkylaminomethylene)-malononitriles and not the expected 3-dialkylaminoisothiazole-4-carbonitriles. Finally, the 3-bromoisothiazole **3** is readily converted into both 3-bromoisothiazole-4-carboxamide **19** and the carboxylic acid **20**. All products are fully characterized.

1. Introduction

Various isothiazoles display wide-ranging biological activity: some are potential anticancer agents which act via inhibition of the MEK-1 and MEK-2 kinases,[1] while others are useful prodrugs for the treatment of hyperproliferative disorders,[2] and as new active site inhibitors for the hepatitis C virus NS5B polymerase.[3] Commercially important isothiazoles include the Kathon® preservatives, the artificial sweetener saccharin and the antibacterial sulfa drug, sulfasomizole. The chemistry and biological uses of the system have been reviewed extensively.[4] Most synthetic strategies involve construction of the isothiazole ring with the desired carbon substituents in place, and the routes are therefore product specific.[4e]

Fully substituted 3,5-dibromo- and dichloroisothiazole-4-carbonitriles **1** and **2** are useful isothiazole scaffolds that are readily prepared in two steps starting from malononitrile and carbon disulfide, followed by treatment of the formed 2,2-dicyanoethene-1,1-bis(thiolate)[5] with either liquid bromine or chlorine gas.[6] These isothiazoles undergo regioselective nucleophilic displacement[6a,7] and also palladium catalyzed C–C coupling (Suzuki, Stille, Negishi, Sonogashira, and Ullmann couplings) at C-5.[7e,8] Furthermore, 3,5-dichloroisothiazole-4-carbonitrile **2** can be methylated using methanesulfonyl fluoride (magic methyl) to give 4-cyano-3,5-dichloro-2-methylisothiazolium fluorosulfonate, which can control the growth of bacteria and fungi.[9] 3,5-Dihaloisothiazole-4-carbonitriles **1** and **2** can act as scaffolds for 5-arylisothiazole-4-carbonitriles[7e,8] that are important due to their broad antiviral activity,[10] and also as scaffolds for the preparation of 3,4,5-triarylisothiazoles.[11]



1 (Hal = Br)
2 (Hal = Cl)

3 (Hal = Br)
4 (Hal = Cl)

5 (R = CO_2H, Hal = Cl)
6 (R = CN, Hal = Br or Cl)

3-Haloisothiazole-4-carbonitriles **3** and **4** are potentially useful isothiazole building blocks and we required access to these as part of our on-going isothiazole studies. To the best of our knowledge the preparation of 3-bromoisothiazole-4-carbonitrile **3** has not been reported and while 3-chloroisothiazole-4-carbonitrile **4** has been prepared in good yield (76%) from the protodecarboxylation of 3-chloro-4-cyanoisothiazole-5-carboxylic acid **5**[8b] this route required access to 3-haloisothiazole-4,5-dicarbonitriles **6**[12] and was considered expensive. As such, we investigated the regioselective hydrodehalogenation of 3,5-dihaloisothiazole-4-carbonitriles **1** (Hal=Br) and **2** (Hal=Cl) with the objective of developing a gram scale and inexpensive route to 3-haloisothiazole-4-carbonitriles **3** (Hal=Br) and **4** (Hal=Cl), respectively.

2. Results and discussion

A wide variety of hydrodehalogenation systems have been developed over the years.[13] In mixed halogen systems the ease of hydrodehalogenation follows the order of I>Br>Cl≥F in line with the

* Corresponding author. Tel.: +357 22 892783; fax: +357 22 892809; e-mail address: koutenti@ucy.ac.cy (P.A. Koutentis).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.03.065

C–Hal bond dissociation energies.[14] Interestingly, there are comparatively few examples of regioselective hydrodehalogenations and typically the halogen most susceptible to nucleophilic displacement suffers hydrodehalogenation first.[15] As such, hydrodehalogenation of 3,5-dibromo- and dichloroisothiazole-4-carbonitriles **1** and **2** was expected to occur regioselectively at C-5, since the C-5 halogen was by far the most susceptible to nucleophilic displacement.[6a,7]

2.1. C-5 Hydrodebromination of 3,5-dibromoisothiazole-4-carbonitrile 1

Initially we focused our attention on the 3,5-dibromoisothiazole-4-carbonitrile **1**. Reducing agents, such as $NaBH_4$ in MeOH, H_2 or HCO_2H with Pd/C and Et_3N, *i*-PrOH with Mg, or $SnCl_2$ in DCM failed to give any product and the starting isothiazole could be recovered, while the use of thiourea in EtOH at ca. 20 °C led to intractable polar products (baseline on TLC). Nevertheless, a successful hydrodebromination was achieved with the use of Zn powder (2 equiv) in refluxing AcOH for 1 h and with In powder (2 equiv) in refluxing H_2O for 24 h or in refluxing HCO_2H for 2 h affording 3-bromoisothiazole-4-carbonitrile **3** in moderate yields of 40, 53 and 40%, respectively. In all cases hydrogen sulfide (H_2S) was detected indicating reductive cleavage of the isothiazole ring. The reaction conditions were partially optimized with respect to the metal and its equivalents, the solvent (hydrogen source) and the reaction temperature.

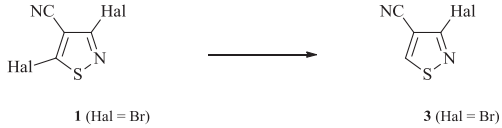
Reductive ring cleavage (formation of H_2S) was avoided by performing the hydrodebromination at low reaction temperatures (ca. 10–15 °C), however, this required the addition of at least 5 equiv of either Zn or In powder to get good product yields. In this regard switching from acetic (mp 16.5 °C, pK_a 4.76) to formic acid (mp 8.4 °C, pK_a 3.75) led to significantly improved reaction times and product yields (Table 1), presumably as the latter acid not only was a better hydrogen source,[16] but also had a lower melting point facilitating its use at these lower reaction temperatures. Reducing the equivalents led to longer reaction times and in most cases unreacted isothiazole was recovered even after 24 h, while increasing the equivalents of Zn (10 equiv) improved the reaction times but lowered the product yields significantly.

Interestingly, switching to the significantly stronger trifluoroacetic acid (TFA) (pK_a 0.65) led to predominantly unreacted isothiazole even after extended reaction times. It has been reported that hydrodehalogenations using strong acids (e.g., HCl) with Zn can fail owing to the extremely rapid rates of hydrogen evolution.[17] On scaling the reaction of 3,5-dibromoisothiazole-4-carbonitrile **1** (200 mg, 0.75 mmol) with either Zn or In (5 equiv) in formic acid, the advantageous yields seen with the use of In powder on the smaller scales became negligible (74 vs 78%, respectively). In light of the relative costs of Zn and In we subsequently carried out the hydrodebromination reaction on a 1 g scale only using Zn powder to get the target 3-bromoisothiazole-4-carbonitrile **3** in 70% yield without the need for chromatography.

The best conditions Zn or In (5 equiv), formic acid, 10–15 °C were then applied to the 3,5-dichloro analogue **2**, however, when treated with Zn powder (5 equiv) the reaction failed to reach completion even after 24 h. When additional Zn (2.5 equiv) was used the reaction was completed in 2 h but the desired product **4** was isolated in low yield (15–23%) and a strong odour of H_2S was noticeable indicating reductive ring cleavage. When In (5 equiv) was used almost no reaction was observed. Indium has a lower reduction potential than zinc [−0.763 (Zn) versus −0.338 V (In)] and is considered to be a more selective reagent.[18]

Presumably, the bond dissociation energies of the C–Cl (397), C–Br (280), and C–S (272 kJ mol^{-1})[19] bonds played a role in the release of H_2S. In the presence of a chlorine atom at C-5 and thus a significantly stronger bond, reductive ring cleavage presumably became competitive. In light of this we searched for an alternative route to 3-chloroisothiazole-4-carbonitrile **4** by either Sandmeyer hydrodeamination of 5-amino-3-chloroisothiazole-4-carbonitrile **7** or by Sandmeyer hydrodehalogenation of either 5-bromo or 5-iodo substituted 3-chloroisothiazole-4-carbonitriles **8** and **9**.

Table 1
Reaction of 3,5-dihaloisothiazole-4-carbonitriles **1** and **2** (0.25 mmol) with Zn or In (5 equiv) in neat acid (1 mL) at 10–15 °C



1 (Hal = Br)
2 (Hal = Cl)

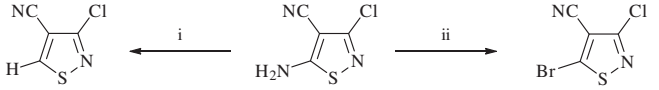
3 (Hal = Br)
4 (Hal = Cl)

Hal	Metal	Acid	Time	Yields **3** and **4** (%)
Br	Zn	AcOH	24	**3** (59)
Br	Zn	HCO_2H	0.17	**3** (66)
Br	Zn	TFA	24	[a]
Cl	Zn[b]	HCO_2H	1	**4** (15)
Br	In	AcOH	22	**3** (67)
Br	In	HCO_2H	3.50	**3** (93)
Br	In	HCO_2H	5.50	**3** (78)
Cl	In	HCO_2H	24	**4** (traces)
Br	Zn	HCO_2H	0.15	**3** (74)[c]
Br	Zn	HCO_2H	0.33	**3** (70)[d]

[a] Incomplete, complex reaction, mainly starting isothiazole.
[b] 7.5 equiv (on a 1 g scale yield rose to 23%).
[c] 200 mg scale based on starting isothiazole/acid (3 mL).
[d] 1 g scale based on the starting isothiazole/acid (15 mL).

2.2. Sandmeyer reactions of 5-amino-3-chloroisothiazole-4-carbonitrile 7

5-Amino-3-chloroisothiazole-4-carbonitrile **7** can be readily prepared and isolated chromatography free by treating 3,5-dichloroisothiazole-4-carbonitrile **2** with dry ammonia in THF.[6a] Sandmeyer chemistry could afford the desired 3-chloroisothiazole **4** either directly via a hydrodeamination or indirectly via a halodeamination followed by hydrodehalogenation. Reaction of 5-amino-3-chloroisothiazole-4-carbonitrile **7** with isoamyl nitrite (6 equiv) in $MeNO_2$ at ca. 20 °C for 10 min, gave the desired 3-chloroisothiazole-4-carbonitrile **4** in 95% yield. When MeCN was used as the solvent the reaction at ca. 20 °C gave the desired product in 65% (20 min reaction) while at reflux the product was isolated in 96% yield (10 min) (Scheme 1).



4 (95%) **7** **8** (69%)

Scheme 1. Reagents and conditions: (i) *i*-Amyl ONO (6 equiv), $MeNO_2$, ca. 20 °C, 10 min, 95%; (ii) *i*-amyl ONO (6 equiv), Br_2 (10 equiv), $MeNO_2$, ca. 20 °C, 10 min, 69%.

The Sandmeyer iododeamination of 5-amino-3-chloroisothiazole-4-carbonitrile **7** using isoamyl nitrite and iodine was reported earlier.[8b] Similar treatment of 5-amino-3-chloroisothiazole-4-carbonitrile **7** with isoamyl nitrite (6 equiv) and dibromine (10 equiv) in nitromethane gave 5-bromo-3-chloroisothiazole-4-carbonitrile **8** in 69% yield together with traces of 3-chloroisothiazole-4-carbonitrile **4** (Scheme 1). The use of less isoamyl nitrite or less dibromine led to more hydrodeamination product and lower yields of the

halodeaminated isothiazole. With access to both the 5-bromo and the 5-iodo-3-chloroisothiazole-4-carbonitriles **8** and **9** the above hydrodehalogenation conditions could be compared directly against the series I versus Br versus Cl.

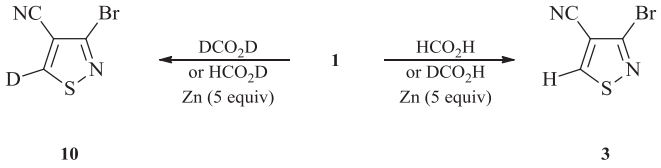
Hydrodehalogenation of either 5-bromo or 5-iodo 3-chloroisothiazole-4-carbonitriles **8** and **9** in neat formic acid with Zn powder (5 equiv) gave 3-chloroisothiazole-4-carbonitrile **4** in 77 and 51% yields, respectively. The latter hydrodeiodination gave a strong odour of H_2S indicating isothiazole ring cleavage and possibly accounted for the moderate yield of product. This could be owed to a possible exothermic reaction, as such, the reaction was repeated with less Zn (3 equiv) over a 25 min period, however, no improvement in the yield was observed (56%). Nevertheless, switching back to the less reactive AcOH using Zn (3 equiv) gave a slightly slower reaction (40 min) and afforded the desired product **4** in 86% yield. The analogous reactions with In powder (5 equiv) took slightly longer but gave the hydrodebrominated and hydrodeiodinated products in good yields, 75 and 86% yields, respectively (Table 2).

2.3. Synthesis of 3-bromo-5-deuterioisothiazole-4-carbonitrile 10

There are many examples of reductions using Zn/AcOH[20] and the hydrogen transferred is considered to be that of the hydroxyl acid.[21] However, in the analogous reaction with Zn/HCO_2H there was some ambiguity.[22] Formic acid is a known hydrogen source and when palladium[23] or rhodium[24] is used as catalyst then both hydrogens, formyl, and hydroxyl, can be transferred.

In light of the above we investigated the reaction of 3,5-dibromoisothiazole-4-carbonitrile **1** with Zn powder (5 equiv) and various commercial deuterated formic acids DCO_2H and HCO_2D in an effort to elucidate which hydrogen or deuterium, formyl or hydroxyl or both, transferred to the isothiazole. Initially, 3,5-dibromoisothiazole-4-carbonitrile **1** treated with zinc (5 equiv) and commercially available deuterated formic acid DCO_2D (98 atom % D) was shown to afford 3-bromo-5-deuterioisothiazole-4-carbonitrile **10** in good yield (71%). Mass spectrometry (EI) of the crude product (prior to recrystallization) indicated the parent ion peaks at *m*/*z* 188 (3), 189 (86), 190 (8), 191 (90), and 192 Da (5%). The ratios suggested very little 3-bromoisothiazole-4-carbonitrile **3** was present. ^1H and ^{13}C NMR spectroscopy showed no signal for H-5, and the $^1J_{CD}$ 29.4 Hz splitting could be observed. Furthermore, in the FTIR the ν(C–H) 3100 cm^{-1} stretch of 3-bromoisothiazole-4-carbonitrile **3** was replaced by the ν(C-D) 2315 cm^{-1} stretch of 3-bromo-5-deuterioisothiazole-4-carbonitrile **10**. With pure samples of both 3-bromoisothiazole-4-carbonitrile **3** and 3-bromo-5-deuterioisothiazole-4-carbonitrile **10** we subsequently investigated the use of DCO_2H and HCO_2D, both 98 atom % D.

Treating 3,5-dibromoisothiazole-4-carbonitrile **1** with Zn (5 equiv) and HCO_2D gave 3-bromo-5-deuterioisothiazole-4-carbonitrile **10** in 60% yield, identical to that described above with no significant trace (by MS, IR, and NMR) of the non-deuterated isothiazole **3**. However, when the reaction was repeated using DCO_2H instead of HCO_2D, 3-bromoisothiazole-4-carbonitrile **3** was the only product (58%) (Scheme 2). In both cases ^1H, ^{13}C NMR, and FTIR spectroscopy and EI mass spectrometry studies on the reaction products were carried out prior to recrystallization. Furthermore, control studies revealed that pure samples of 3-bromo-5-deuterioisothiazole-4-carbonitrile **10** and 3-bromoisothiazole-4-carbonitrile **3** treated with HCO_2H and DCO_2D, respectively, at ca. 20 °C for 1 h (with and without Zn dust) did not suffer any hydrogen–deuterium exchange (by MS and NMR).

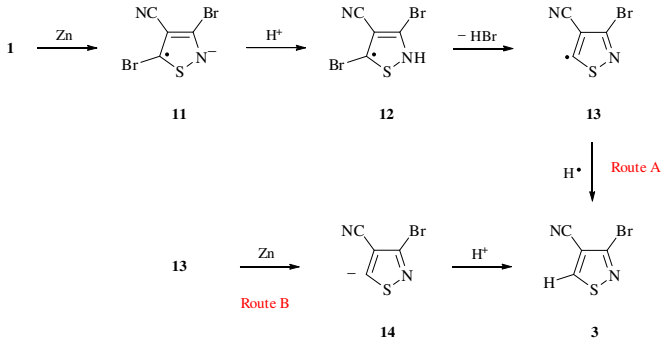


10 **3**

Scheme 2.

The above results, suggested that the hydrogen transferred from the formic acid to the isothiazole originated only from the hydroxyl and not the formyl group. Formally, this could be considered a protodehalogenation but this may be misleading. Furthermore, in reviewing the literature we find the terms hydro and protodehalogenation used rather indiscriminately.[25]

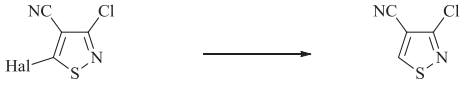
Several mechanisms can be proposed: single electron transfer from zinc to isothiazole can form the radical anion **11** and subsequent protonation by the formic acid can give radical **12**. Elimination of HBr would afford the aromatic isothiazole radical **13**, which could either accept an adsorbed 'nascent' hydrogen radical (route A) to give the isothiazole **3** or another electron from the Zn to form anion **14** that protonates to afford the observed product **3**, i.e., protodehalogenation (route B)[26] (Scheme 3). In the former case this would imply that all the available adsorbed hydrogen was either H in the case of DCO_2H or D when HCO_2D was used.



Scheme 3.

Our understanding of adsorbed or 'nascent' hydrogen is hydrogen chemisorbed onto the surface of the zinc that can be transferred to chemisorbed neighboring isothiazole.[27] Formic acid can undergo reduction by zinc to give hydrogen and formate chemisorbed onto the zinc surface. The possibility, however, that

Table 2
Reaction of 5-halo-3-chloroisothiazole-4-carbonitriles **2**, **8**, and **9** (0.25 mmol) with Zn or In in HCO_2H (1 mL) at 10–15 °C



2 (Hal = Cl)
8 (Hal = Br)
9 (Hal = I)

4

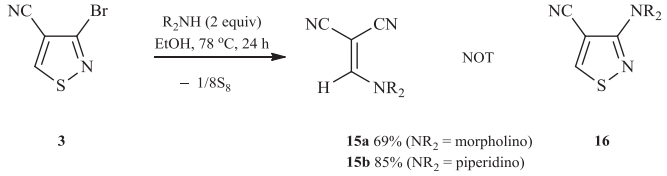
Hal	Metal (equiv)	Time (h)	Yield **4** (%)
Cl	Zn (7.5)	2	15
Br	Zn (5)	0.67	77
I	Zn (5)	0.25	51
I	Zn (3)	0.42	56
I	Zn (3)[a]	0.67	86
Cl	In (5)	24	Trace
Br	In (5)	5.5	75
I	In (5)	1	86

[a] AcOH was used instead of HCO_2H.

the formic acid dissociates to give both formyl and hydroxyl hydrogens cannot be eliminated, since there could be a rapid exchange of chemisorbed hydrogen species (H or D) with the formic acid protons (H^+ or D^+) in the bulk solvent.[28] As such this apparent protodehalogenation may in fact be a hydrodehalogenation or pseudo protodehalogenation.

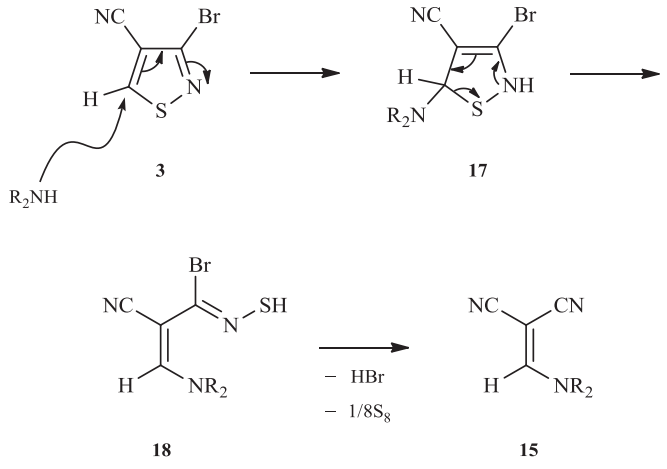
2.4. Reactions of 3-bromoisothiazole-4-carbonitrile 3

With 3-bromoisothiazole-4-carbonitrile **3** in hand we examined its behavior toward various heteroatom nucleophiles. Treating the 3-bromoisothiazole **3** with either sodium methoxide (1.5 equiv) in methanol at ca. 70 °C for 4 h led to a complex reaction mixture from which no identifiable product could be isolated, while treatment with thiophenol (2 equiv) and DBU (1 equiv) or Hünig's base (1 equiv) in benzene at reflux gave an intractable reaction mixture. Nevertheless, when 3-bromoisothiazole-4-carbonitrile **3** was treated with either morpholine or piperidine (4 equiv) in EtOH at ca. 78 °C for 24 h the reactions gave elemental sulfur (80–87%) and the ring opened 2-(dialkylaminomethylene)malononitriles **15a** and **b** in 71 and 84% yields, respectively, not the expected 3-(dialkylamino)isothiazoles **16** (Scheme 4). Fewer equivalents of dialkylamine led to incomplete reactions.



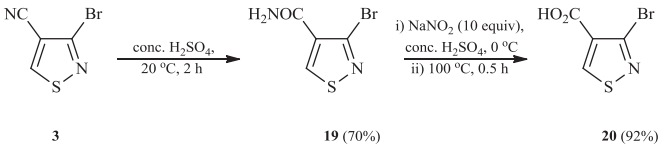
Scheme 4.

This was not completely unexpected; isothiazoles are more prone to nucleophilic attack at C-5 and also at the ring sulfur rather than at C-3.[4e] As such, we suspect the amines attack the isothiazole at C-5 to give adduct **17**, which subsequently fragments to the thiol **18** that presumably loses elemental sulfur through a sulfur chain extension mechanism (Scheme 5).[29] Direct attack by the amine on the ring sulfur could be dismissed owing to the absence of bis (dialkylamino)sulfide in the reaction mixture and the isolation of significant amounts of elemental sulfur (80–87%).



Scheme 5.

Attempts to brominate 3-bromoisothiazole-5-carbonitrile **3** at C-5 using NBS or Br_2 (2 equiv) in AcOH or in CCl_4 at 60 °C, failed to give any reaction even after 24 h. Nevertheless, under acidic conditions, concentrated sulfuric acid at ca. 20 °C for 2 h, the cyano hydrated to give the expected 3-bromoisothiazole-4-carboxamide **19** in 70% yield. The latter was reacted with $NaNO_2$ (10 equiv) in H_2SO_4 at 0–100 °C[11] to give after 0.5 h the 3-bromoisothiazole-4-carboxylic acid **20** in 92% yield (Scheme 6).



Scheme 6.

The latter reactions demonstrated that while nucleophilic displacement at C-3 was not achieved, further functionalization at the C-4 nitrile was possible and that the C-5 position was not susceptible to electrophilic substitution.

3. Conclusions

A regioselective dehalogenation on 3,5-dihaloisothiazole-4-carbonitriles **1** and **2** using zinc or indium powder in formic acid, was achieved affording 3-haloisothiazole-4-carbonitriles in good yields. 5-Chloro, bromo, and iodo 3-chloroisothiazole-4-carbonitriles suffered hydrodehalogenation exclusively at C-5. Use of deuterated formic acids (DCO_2D and HCO_2D) afforded the 3-bromo-5-deuterioisothiazole-4-carbonitrile **8** in good yield while use of DCO_2H gave only 3-bromoisothiazole-4-carbonitrile **3**. Attempted nucleophilic displacement of the 3-bromo substituent using cyclic dialkylamines led only to the ring opened 2-(dialkylaminomethylene)malononitriles **15** and elemental sulfur, while the C-4 nitrile could be manipulated readily to give both the carboxamide and the carboxylic acid in high yield.

4. Experimental

4.1. General procedures

All chemicals were commercially available except those whose synthesis is described. Anhydrous Na_2SO_4 was used for drying organic extracts and all volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by TLC using commercial glass backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography was used throughout for all non-TLC scale chromatographic separations using Merck Silica Gel 60 (less than 0.063 mm).[30] Melting points were determined using a PolyTherm-A, Wagner & Munz, Koefler—Hotstage Microscope apparatus or were determined using a TA Instruments DSC Q1000 with samples hermetically sealed in aluminum pans under an argon atmosphere; using heating rates of 5 °C/min (DSC mp listed by *onset* and *peak* values). Solvents used for recrystallization are indicated after the melting point. UV spectra were obtained using a Perkin–Elmer Lambda-25 UV/vis spectrophotometer and inflections are identified by the abbreviation 'inf'. IR spectra were recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer with Pike *Miracle* Ge ATR accessory and strong, medium and weak peaks are represented by s, m, and w, respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 machine (at 500 and 125 MHz, respectively). Deuterated solvents were used for homonuclear lock

and the signals are referenced to the deuterated solvent peaks. CH assignments are made based on DEPT 135 spectroscopy. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GC–MS with direct inlet probe. 3,5-Dibromoisothiazole-4-carbonitrile **1**,[6a] 3,5-dichloroisothiazole-4-carbonitrile **2**,[6a] 5-amino-3-chloroisothiazole-4-carbonitrile **7**,[6a] and 3-chloro-5-iodoisothiazole-4-carbonitrile **9**[8b] were prepared according to literature procedures. DCO_2D, DCO_2H, and HCO_2D were commercially sourced and contained 98 atom % D.

4.1.1. Hydrodehalogenations of 3,5-dihaloisothiazoles *1* and *2*.

*4.1.1.1. 3-Bromoisothiazole-4-carbonitrile **3**.* To a mixture of 3,5-dibromoisothiazole-4-carbonitrile **1** (67 mg, 0.25 mmol) and Zn dust (81.7 mg, 1.25 mmol) at ca. 10 °C was added cold (ca. 15 °C) HCO_2H (1 mL) and stirred for 10 min at 10–15 °C. After the reaction was finished (TLC) the mixture was filtered and the filtrate extracted with DCM (20 mL) and water (5 mL). The organic phase was dried (Na_2SO_4), filtered and the volatiles removed in vacuo to afford the *title compound* **3** (31 mg, 66%) as colorless long needles, mp 47.5–48.5 °C (from pentane) DSC (onset) 54.0 °C (peak) 54.9 °C, R_f 0.33 (hexane/DCM, 1:1); (found: C, 25.6; H, 0.5; N, 14.8. C_4HBrN_2S requires C, 25.4; H, 0.5; N, 14.8%); λ_{max} (DCM)/nm 264 (log ε 4.05); ν_{max}/cm^{-1} 3100m (Ar C–H), 2241m (C≡N), 1487m, 1352w, 1323s, 1144m, 1026m, 868s, 831s, 804m, 764m; δ_H (300 MHz; $CDCl_3$) 9.16 (1H, s, *H*-5); δ_C (75 MHz; $CDCl_3$) 158.2 (*C*-5), 139.2 (*C*-3), 113.2, 111.5; *m*/*z* (EI) 190 (M^++2, 100%), 188 (M^+, 97), 139 (25), 137 (25), 109 (7), 83 (82), 58 (10), 51 (14), 45 (36). Similarly, treating 3,5-dibromoisothiazole-4-carbonitrile **1** (1 g, 3.6 mmol) with Zn powder (1.22 g, 18.7 mmol) in HCO_2H (15 mL) gave the *title compound* **3** (493 mg, 70%) as colorless needles identical to that described above.

*4.1.1.2. 3-Chloroisothiazole-4-carbonitrile **4**. Typical procedure* (Table 1). To a mixture of 3,5-dichloroisothiazole-4-carbonitrile **2** (45 mg, 0.25 mmol) and Zn dust (123 mg, 1.88 mmol) at ca. 10 °C was added cold (ca. 15 °C) HCO_2H (1 mL) and stirred for 1 h at 10–15 °C. After the reaction was finished (TLC) the mixture was filtered and the filtrate extracted with DCM (20 mL) and water (5 mL). The organic phase was dried (Na_2SO_4), filtered and the volatiles removed in vacuo to afford the *title compound* **4** (5.5 mg, 15%) as colorless long needles, mp 50–51 °C (from pentane) (lit.[8b] 50–51 °C), R_f 0.33 (hexane/DCM, 1:1) identical to an authentic sample.

4.1.2. Sandmeyer reactions.

*4.1.2.1. 3-Chloroisothiazole-4-carbonitrile **4** from 5-amino-3-chloroisothiazole-4-carbonitrile **7**.* To a mixture of isoamyl nitrite (5.1 mL, 37.8 mmol) in $MeNO_2$ (5 mL) at ca. 20 °C, a solution of 5-amino-3-chloroisothiazole-4-carbonitrile **7** (1 g, 6.3 mmol) in $MeNO_2$ (5 mL) was added and the reaction mixture was stirred for 10 min. After the reaction was finished (TLC), the mixture was diluted with DCM (50 mL) and extracted with water (50 mL). The organic phase was dried (Na_2SO_4), filtered, adsorbed onto silica and chromatographed (DCM) to afford the *title compound* **4** (870 mg, 96%) as colorless needles, mp 50–51 °C (from pentane) (lit.[8b] 50–51 °C), R_f 0.33 (hexane/DCM, 1:1) identical to an authentic sample.

*4.1.2.2. 5-Bromo-3-chloroisothiazole-4-carbonitrile **8**.* To a mixture of isoamyl nitrite (2.55 mL, 18.9 mmol) and Br_2 (1.6 mL, 31 mmol) in $MeNO_2$ (2 mL) at ca. 20 °C, a solution of 5-amino-3-chloroisothiazole-4-carbonitrile **7** (0.5 g, 3.1 mmol) in $MeNO_2$ (2 mL) was added and the reaction mixture was stirred for 10 min. After the reaction was finished (TLC), the mixture was diluted with DCM (50 mL), washed with $Na_2S_2O_3$ (500 mg, 32 mmol) and extracted with water (50 mL). The organic phase was dried (Na_2SO_4), filtered, adsorbed onto silica, and chromatographed (hexane) to afford the *title compound* **8** (486 mg, 69%) as colorless plates, mp 94.5–95.5 °C (from cyclohexane), R_f 0.56 (hexane/DCM, 1:1); (found: C, 21.6; H, <0.1; N, 12.5. C_4BrClN_2S requires C, 21.5; H, 0.0; N, 12.5%); λ_{max} (DCM)/nm 250 (log ε 4.06), 263 (4.08), 268 inf (4.04); ν_{max}/cm^{-1} 2237m (C≡N), 1495s, 1331s, 1090w, 970m, 816s, 793m; δ_C (75 MHz; $CDCl_3$) 151.0, 147.3, 113.5, 110.1; *m*/*z* (EI) 226 (M^++4, 10%), 224 (M^++2, 38), 222 (M^+, 30), 173 (31), 171 (86), 163 (11), 161 (11), 143 (M^+-Br, 22), 108 (20), 82 (82), 71 (52), 69 (23), 57 (32), 55 (18), 51 (20), 49 (53).

4.1.3. Hydrodehalogenation of mixed dihaloisothiazoles *8* and *9*.

*4.1.3.1. 3-Chloroisothiazole-4-carbonitrile **4** from 5-bromo-3-chloroisothiazole-4-carbonitrile **8**.* To a mixture of 5-bromo-3-chloroisothiazole-4-carbonitrile **8** (56 mg, 0.25 mmol) and Zn dust (81.7 mg, 1.25 mmol) at ca. 10 °C was added cold (ca. 15 °C) HCO_2H (1 mL) and stirred for 40 min at ca. 10–15 °C. After the reaction was finished (TLC) the mixture was filtered and the filtrate extracted with DCM (20 mL) and water (5 mL). The organic phase was dried (Na_2SO_4), filtered and the volatiles removed in vacuo to afford the *title compound* **4** (28 mg, 77%) as colorless long needles, mp 50–51 °C (from pentane) (lit.[8b] 50–51 °C), identical to an authentic sample.

*4.1.3.2. 3-Chloroisothiazole-4-carbonitrile **4** from 3-chloro-5-iodoisothiazole-4-carbonitrile **9**.* To a mixture of 3-chloro-5-iodoisothiazole-4-carbonitrile **9** (68 mg, 0.25 mmol) and Zn dust (81.7 mg, 1.25 mmol) at ca. 10 °C was added cold (ca. 15 °C) HCO_2H (1 mL) and stirred for 15 min at 10–15 °C. After the reaction was finished (TLC) the mixture was filtered and the filtrate extracted with DCM (20 mL) and water (5 mL). The organic phase was dried (Na_2SO_4), filtered and the volatiles removed in vacuo to afford the *title compound* **4** (18.5 mg, 51%) as colorless long needles, mp 50–51 °C (from pentane) (lit.[8b] 50–51 °C) identical to an authentic sample.

4.1.4. Reactions with deuterated formic acids.

*4.1.4.1. 3-Bromo-5-deuterioisothiazole-4-carbonitrile **10**.* To a mixture of 3,5-dibromoisothiazole-4-carbonitrile **1** (67 mg, 0.25 mmol) and Zn dust (81.7 mg, 1.25 mmol) at ca. 10 °C was added cold (ca. 15 °C) DCO_2D (1 mL) and stirred at 10–15 °C. After the reaction was finished (TLC) the mixture was filtered and the filtrate extracted with DCM (20 mL) and water (10 mL). The organic phase was dried (Na_2SO_4), filtered and the volatiles removed in vacuo to afford the *title compound* **10** (34 mg, 71%) as colorless long needles, mp 46–46.5 °C (from pentane) DSC (onset) 53.9 °C (peak) 54.8 °C, R_f 0.33 (hexane/DCM, 1:1); (found: C, 25.3; H, 1.0; N, 14.6. C_4DBrN_2S requires C, 25.3; H, 1.1; N, 14.7%); λ_{max} (DCM)/nm 263 (log ε 4.36); ν_{max}/cm^{-1} 2315m (Ar CD), 2239m (C≡N), 1476s, 1354w, 1346w, 1315s, 1034m, 1016m, 986m, 804s, 766s; δ_C (125 MHz; $CDCl_3$) 158.0 (t, $^1J_{CD}$ 29.8, *C*-5), 139.3 (*C*-4), 113.1, 111.5; *m*/*z* (EI) 191 (M^++2, 90%), 189 (M^+, 86), 139 (28), 137 (30), 110 (9), 84 (100), 82 (49), 58 (22), 52 (20), 46 (57). Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **1** with HCO_2D gave the *title compound* **10** (28.5 mg, 60%) as colorless needles, mp 46–46.5 °C (from pentane) identical to that described above.

*4.1.4.2. 3-Bromoisothiazole-4-carbonitrile **3** from DCO_2H reaction.* Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **1** (67 mg, 0.25 mmol) with Zn dust (81.7 mg, 1.25 mmol) and DCO_2H (1 mL) gave the *title compound* **3** as colorless needles, mp 47.5–48.5 °C (from pentane), identical to that described above.

4.1.5. Reactions of 3-bromoisothiazole-4-carbonitrile ***3****.*

4.1.5.1. 2-(Morpholinomethylene)malononitrile ***15a****. Typical procedure*. A stirred mixture of 3-bromoisothiazole-4-carbonitrile **3** (25 mg, 0.13 mmol) and morpholine (45 μL, 0.52 mmol) in EtOH (1 mL) was heated at ca. 78 °C under reflux until no starting material remained (TLC). The reaction mixture was adsorbed onto silica and chromatographed (hexane) to afford elemental sulfur (3.3 mg, 80%) as yellow needles, mp 114–115 °C, R_f 0.76 (hexane). Further elution (hexane/DCM, 1:4) gave the *title compound* **15a** (15 mg, 71%) as beige flakes, mp 138–140 °C (from EtOH/pentane) [lit.[31] 149–150 °C (from EtOH)], R_f 0.43 (DCM/*t*-BuOMe, 9:1); ν_{max}/cm^{-1} 2982w, 2874w, 2208m and 2197m (C≡N), 1632s (C=C), 1466w, 1454m, 1439m, 1375w, 1354m, 1310w, 1285w, 1250m, 1119s, 1080w, 1026m, 1011m, 974w, 937w, 870s, 779w; δ_H (300 MHz; $CDCl_3$) 7.02 (1H, s, C-*H*), 3.95 (2H, br s, NCH_2), 3.79 (4H, dd *J* 4.9, 4.7, OCH_2), 3.49 (2H, br s, NCH_2); *m*/*z* (EI) 163 (M$^+$, 47%), 105 (37), 91 (7), 78 (80), 57 (39), 51 (9), 42 (100).

4.1.5.2. 2-(Piperidin-1-ylmethylene)malononitrile ***15b****.* Similar treatment of 3-bromoisothiazole-4-carbonitrile **3** (25 mg, 0.13 mmol) with piperidine (51 μL, 0.52 mmol) afforded elemental sulfur (3.7 mg, 87%) as yellow needles, mp 114–115 °C; R_f 0.76 (hexane) and then the *title compound* **15b** (18 mg, 84%) as light orange needles, mp 85.5–86.5 °C (from EtOH/pentane) [lit.[32] 90–91 °C (from EtOAc/pentane)], R_f 0.84 (DCM/t-BuOMe, 9:1); ν_{max}/cm^{-1} 2947w, 2208m and 2195m (C≡N), 1618s (C=C), 1470w, 1441w, 1362m, 1346m, 1269w, 1256w, 1217w, 1179w, 1098w, 1024m, 997w, 968w, 945w, 854w, 764m; δ_H (300 MHz; $CDCl_3$) 6.96 (1H, s, =C–*H*), 3.86 (2H, br s, NCH_2), 3.43 (2H, br s, NCH_2), 1.73 (6H, br s, 3×CH_2); *m*/*z* (EI) 161 (M$^+$, 100%), 146 (13), 132 (32), 120 (26), 106 (32), 94 (11), 83 (73), 78 (43), 67 (13), 57 (29), 41 (65).

4.1.5.3. 3-Bromoisothiazole-4-carboxamide ***19****.* A mixture of 3-bromoisothiazole-4-carbonitrile **3** (25 mg, 0.13 mmol) in c. H_2SO_4 (1 mL) was stirred at ca. 20 °C for 2 h until no starting material remained (TLC). After the reaction was finished, the reaction mixture was poured onto crushed ice and extracted with *t*-BuOMe (2×50 mL). The organic layers were combined, dried (Na_2SO_4), and evaporated in vacuo to afford the *title compound* **19** (15 mg, 70%) as colorless needles, mp 138–141 °C (from PhH), R_f 0.47 (*t*-BuOMe); (found: C, 23.3; H, 1.4; N, 13.4. $C_4H_3BrN_2OS$ requires C, 23.2; H, 1.5; N, 13.5%); λ_{max} (DCM)/nm 228 (log ε 3.44), 258 (3.96); ν_{max}/cm^{-1} 3381w (NH), 3289w, 3188w, 3102w, 1655s (C=O), 1612m, 1506m, 1406m, 1344w, 1294m, 1140w, 1120m, 1003m, 864w, 822w, 812w, 779w; δ_H (300 MHz; DMSO-d_6) 9.32 (1H, s, *H*-5), 7.96 (1H, br s, N*H*), 7.59 (1H, br s, N*H*); δ_C (75 MHz; DMSO-d_6) 162.4 (*C*=O), 153.4 (*C*-5), 136.1, 133.8; *m*/*z* (EI) 208 (M$^+$+2, 58%), 206 (M$^+$, 59), 192 (99), 190 (100), 164 (3), 162 (3), 127 (15), 113 (5), 111 (9), 85 (20), 83 (22), 57 (32), 52 (9), 44 (65).

4.1.5.4. 3-Bromoisothiazole-4-carboxylic acid ***20****.* To a stirred solution of 3-bromoisothiazole-4-carboxamide **19** (86 mg, 0.41 mmol) in concentrated H_2SO_4 (2 mL) at 0 °C was added in three equal portions $NaNO_2$ (285 mg, 4.1 mmol). The reaction mixture was then heated at ca. 100 °C until no starting material remained (TLC). The mixture was allowed to cool to ca. 20 °C and was poured onto crushed ice to afford a colorless precipitate. The precipitate was filtered, washed (H_2O), and dried in vacuo to give the *title compound* **20** (79.4 mg, 92%) as pale beige plates, mp 195–197 °C (from PhH), R_f 0.44 (*t*-BuOMe); (found: C, 23.2; H, 0.7; N, 6.5. $C_4H_2BrNO_2S$ requires C, 23.1; H, 1.0; N, 6.7%); λ_{max} (DCM)/nm 228 (log ε 3.49), 260 (3.93); ν_{max}/cm^{-1} 3113w, 2947w, 2907w, 2733w, 2602w, 2536w, 1713 (C=O), 1483m, 1435w, 1418w, 1354m, 1333w, 1217s, 1015s, 887m, 849w, 835m; δ_H (300 MHz; DMSO-d_6) O*H* missing, 9.60 (1H, s, *H*-5); δ_C (75 MHz; DMSO-d_6) 161.2 (*C*=O), 159.2, 137.3, 129.6; *m*/*z* (EI) 209 (M$^+$+2, 94%), 207 (M$^+$, 96), 192 (100), 190 (95), 128 (6), 113 (6), 111 (9), 85 (19), 83 (29), 82 (18), 57 (57), 52 (12), 45 (63).

Acknowledgements

The authors wish to thank the Cyprus Research Promotion Foundation [Grant No. ΠΕΝΕΚ/ΕΝΙΣΧ/0308/83] and the following organizations in Cyprus for generous donations of chemicals and glassware: the State General Laboratory, the Agricultural Research Institute, the Ministry of Agriculture and Biotronics Ltd. Furthermore we thank the A.G. Leventis Foundation for helping to establish the NMR facility in the University of Cyprus.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.03.065.

References and notes

1. (a) Varaprasad, C. V. N. S.; Barawkar, D.; Abdellaoui, H. E.; Chakravarty, S.; Allan, M.; Chen, H.; Zhang, W.; Wu, J. Z.; Tam, R.; Hamatake, R.; Lang, S.; Hong, Z. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3975; (b) Abdellaoui, H. E.; Varaprasad, C. V. N. S.; Barawkar, D.; Chakravarty, S.; Maderna, A.; Tam, R.; Chen, H.; Allan, M.; Wu, J. Z.; Appleby, T.; Yan, S.; Zhang, W.; Lang, S.; Yao, N.; Hamatake, R.; Hong, Z. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5561; (c) Melagraki, G.; Afantitis, A.; Sarimveis, H.; Igglessi-Markopoulou, O.; Koutentis, P. A.; Kollias, G. *Chem. Biol. Drug Des.* **2010**, *76*, 397.
2. Larson, E. R.; Noe, M. C.; Gant, T. G. U.S. Patent 6,235,764, 2001.
3. Yan, S.; Appleby, T.; Gunic, E.; Shim, J. H.; Tasu, T.; Kim, H.; Rong, F.; Chen, H.; Hamatake, R.; Wu, J. Z.; Hong, Z.; Yao, N. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 28.
4. (a) Pain, D. L.; Peart, B. J.; Wooldridge, K. R. H. In *Comprehensive Heterocyclic Chemistry I*; Potts, K. T., Chief Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 6; Chapter 4.17, p 131; (b) Chapman, R. F.; Peart, B. J. In *Comprehensive Heterocyclic Chemistry II*; Shinkai, I., Chief Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 3; Chapter 3.05, p 319; (c) Clerici, F.; Gelmi, M. L.; Pellegrino, S. In *Comprehensive Heterocyclic Chemistry III*; Joule, J., Chief Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 4; Chapter 4.05, p 545; (d) Kaberdin, R. V.; Potkin, V. I. *Russ. Chem. Rev.* **2002**, *71*, 673; (e) Brown, D. W.; Sainsbury, M. In *Isothiazoles in Science of Synthesis, Product Class 15*; Schaumann, E., Ed.; Georg Thieme: Stuttgart, 2002; Vol. 11; Chapter 11.15, p 507; (f) Elgazwy, A.-S. S. H. *Tetrahedron* **2003**, *59*, 7445.
5. Morton, B. U.S. Patent 3,057,875, 1962.
6. (a) Hatchard, W. R. *J. Org. Chem.* **1964**, *29*, 660; (b) Hatchard, W. R. U.S. Patent 3,155,679, 1964.
7. (a) Lee, F. T.; Li, B. W.; Volpp, G. P. *J. Heterocycl. Chem.* **1970**, *7*, 941; (b) Walsh, R. J. A.; Wooldridge, K. R. H. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1247; (c) Clarke, K.; Fox, W. R.; Scrowston, R. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1029; (d) Turnbull, M. D.; Smith, A. M.; Salmon, R. U.S. Patent 5,705,516, 1998. (e) Ioannidou, H. A.; Koutentis, P. A. *Tetrahedron* **2009**, *65*, 7023.
8. (a) Christoforou, I. C.; Koutentis, P. A.; Rees, C. W. *Org. Biomol. Chem.* **2003**, *1*, 2900; (b) Christoforou, I. C.; Koutentis, P. A. *Org. Biomol. Chem.* **2006**, *4*, 3681.
9. Virgilio, J. A; Manowitz, M.; Heilweil, E. U.S. Patent 4,281,136, 1981.
10. (a) Cutrὸ, C. C. C.; Garozzo, A.; Siracusa, M. A.; Sarvà, M. C.; Tempera, G.; Geremia, E.; Pinizzotto, M. R.; Guerrera, F. *Bioorg. Med. Chem.* **1998**, *6*, 2271; (b) Cutrὸ, C. C. C.; Garozzo, A.; Siracusa, M. A.; Sarvà, M. C.; Castro, A.; Geremia, E.; Pinizzotto, M. R.; Guerrera, F. *Bioorg. Med. Chem.* **1999**, *7*, 225; (c) Garozzo, A.; Cutrὸ, C. C. C.; Castro, A.; Tempera, G.; Guerrera, F.; Sarvà, M. C.; Geremia, E. *Antiviral Res.* **2000**, *45*, 199; (d) Cutrὸ, C. C. C.; Garozzo, A.; Siracusa, M. A.; Castro, A.; Tempera, G.; Sarvà, M. C.; Guerrera, F. *Antiviral Res.* **2002**, *55*, 357.
11. Christoforou, I. C.; Koutentis, P. A. *Org. Biomol. Chem.* **2007**, *5*, 1381.
12. (a) Christoforou, I. C.; Koutentis, P. A.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1236; (b) Emayan, K.; English, R. F.; Koutentis, P. A.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3345.
13. (a) Pinder, A. R. *Synthesis* **1980**, 425; (b) Urbano, F. J.; Marinas, J. M. *J. Mol. Catal. A: Chem.* **2001**, *173*, 329; (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009.
14. (a) Hudlicky, M. In *Comprehensive Organic Synthesis*; Chief Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8; Chapter 4.5, pp 895–922; (b) Sutherland, A. G. In *Comprehensive Organic Functional Group Transformations*; Roberts, S. M., Chief Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Elsevier: Oxford, 1995; Vol. 1, pp 1–11.
15. (a) Zhang, Y.-M.; Gu, M.; Ma, H.; Tang, J.; Lu, W.; Nan, F.-J. *Chin. J. Chem.* **2008**, *26*, 962; (b) Libnow, S.; Wille, S.; Christiansen, A.; Hein, M.; Reinke, H.; Köckerling, M.; Miethchen, R. *Synthesis* **2006**, 496; (c) Wagner, F. F.; Comins, D. L. *Eur. J. Org. Chem.* **2006**, 3562; (d) Thomsen, B.; Beeley, N.; Sekiguchi, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2565; (e) Bastos, M. M.; Barbosa, J. P.; Pinto, A. C.;

Kover, W. B.; Takeuchi, Y.; Boechat, N. *J. Braz. Chem. Soc.* **2001**, *12*, 417; (f) Kanuma, K.; Omodera, K.; Nishiguchi, M.; Funakoshi, T.; Chaki, S.; Semple, G.; Tran, T.-A.; Kramer, B.; Hsu, D.; Casper, M.; Boarland, M. P. V.; McOmie, J. F. W. *J. Chem. Soc.* **1951**, 1218; (g) Gol'dfarb, Y. L.; Gromova, G. P.; Belen'kii, L. I. *Chem. Heterocycl. Compd.* **1986**, *22*, 663.
16. Gibson, H. W. *Chem. Rev.* **1969**, *69*, 673.
17. Saha, A. K.; Sarkar, A. U.S. Patent 5,051,030, 1991.
18. (a) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633; (b) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017.
19. *CRC Handbook of Chemistry and Physics*, 75th ed.; Lide, D. R., Ed.; CRC: Cleveland, OH, 1994/95; pp 9–52.
20. (a) Johnson, T. B.; Hahn, D. A. *J. Am. Chem. Soc.* **1917**, *39*, 1255; (b) Hartman, W. W.; Roll, L. J. *Org. Synth.* **1943**, *2*, 418; (c) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269; (d) House, H. O.; Larson, J. K. *J. Org. Chem.* **1968**, *33*, 61; Hassner, A.; Hoblitt, R. P.; Heathcock, C.; Kropp, J. E.; Lorber, M. *J. Am. Chem. Soc.* **1970**, *92*, 1326; (e) Di Vona, M. L.; Rosnati, V. *J. Org. Chem.* **1991**, *56*, 4269; (f) Rani, B. R.; Ubukata, M.; Osada, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 282.
21. (a) Schissler, D. O.; Thompson, S. O.; Turkevich, J. *Discuss. Faraday Soc.* **1951**, *10*, 46; (b) Gronowitz, S. *Acta Chem. Scand.* **1959**, *13*, 1045; (c) Yamanaka, H.; Oshima, R.; Teramura, K.; Ando, T. *J. Org. Chem.* **1972**, *37*, 1734.
22. Kowalik, J.; Kupczyk-Subotkowska, L.; Mastalerz, P. *Synthesis* **1981**, 57.
23. (a) Weiner, H.; Blum, J.; Sasson, Y. *J. Org. Chem.* **1991**, *56*, 4481; (b) Yu, J.; Spencer, J. B. *Chem. Commun.* **1998**, 1935; (c) Gao, W.; Keith, J. A.; Anton, J.; Jacob, T. *J. Am. Chem. Soc.* **2010**, *132*, 18377.
24. Leitner, W.; Brown, J. M.; Brunner, H. *J. Am. Chem. Soc.* **1993**, *115*, 152.
25. (a) Bouffard, J.; Eaton, R. F.; Müller, P.; Swager, T. M. *J. Org. Chem.* **2007**, *72*, 10166; (b) Sazonov, P. K.; Artamkina, G. A.; Khrustalev, V. N.; Antipin, M. Y.; Beletskaya, I. P. *J. Organomet. Chem.* **2003**, *681*, 59.
26. (a) Hirasawa, N.; Takahashi, Y.; Fukuda, E.; Sugimoto, O.; Tanji, K.-i. *Tetrahedron Lett.* **2008**, *49*, 1492; (b) Brace, N. O.; Van Elswyk, J. E. *J. Org. Chem.* **1976**, *41*, 766.
27. (a) Laborda, F.; Bolea, E.; Baranguan, M. T.; Castillo, J. R. *Spectrochim. Acta, Part B* **2002**, *57*, 797; (b) Meija, J.; D'Ulivo, A. *Anal. Bioanal. Chem.* **2008**, *391*, 1475; (c) Meija, J.; D'Ulivo, A. *Anal. Bioanal. Chem.* **2008**, *392*, 771.
28. Davis, R. E.; Brown, A. E.; Hopmann, R.; Kibby, C. L. *J. Am. Chem. Soc.* **1963**, *85*, 487.
29. Davis, R. E. *J. Am. Chem. Soc.* **1958**, *80*, 3565.
30. Harwood, L. M. *Aldrichimica Acta* **1985**, *18*, 25.
31. Santilli, A. A.; Bruce, W. F.; Osdene, T. S. *J. Med. Chem.* **1964**, *7*, 68.
32. Sundaramoorthi, R.; Keenan, T. P. *Synth. Commun.* **2007**, *37*, 417.