Facile Synthesis of *N*-Substituted Isothiazol-3(2*H*)-ones Using a Hypervalent Iodine(III) Reagent

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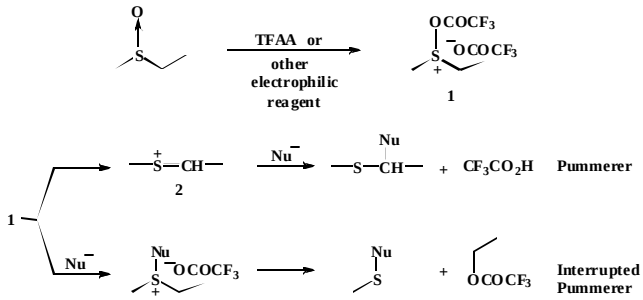
Treatment of *N*-substituted (*Z*)-3-(benzylsulfanyl)propenamides (**4**) with phenyliodine(III) bis(trifluoroacetate) containing trifluoroacetic acid resulted in an interrupted Pummerer-type reaction to give *N*-substituted isothiazol-3(2*H*)-ones (**5**) rather than the normal Pummerer-type products.

INTRODUCTION

The Pummerer reaction of sulfoxides normally proceeds *via* an activated sulfoxide (**1**) and then a thionium ion (**2**) which reacts with a nucleophile at carbon to afford an α-substituted sulfide.[1] In an interrupted Pummerer reaction, the tricoordinate sulfur intermediate (**1**) undergoes reaction with a nucleophile at sulfur leading to unexpected product (Scheme I).[2]

Scheme I



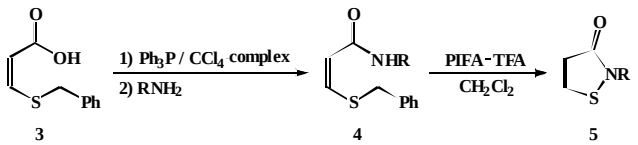
Isothiazol-3(2*H*)-ones have found a range of industrial applications and are widely used as antimicrobial and algicidal additives.[3] The methods used for their synthesis involve the cyclization of cis-3-thiocyanoacrylamides by treatment with acid,[4] oxidative annelation of 3,3′-dithiopropionamides using either chlorine or sulfuryl chloride as oxidant,[5] nucleophilic displacement of *N*-substituted of 5-aroyl-3(2*H*)-isothiazolones by treatment with base,[6] and cyclization of sulfoxide substrates acting as sulfenyl halide equivalents.[7]

Recently, hypervalent iodine reagents have been used extensively in organic synthesis due to their low toxicity, ready availability and easy handling.[8] As a continuation of our studies concerning hypervalent iodine(III) chemistry, we have reported a Pummerer-type reaction that provides a very simple and convenient procedure for the preparation of 4*H*-pyrrolo[2,1-*c*][1,4]benzothiazines by treatment of α-acyl sulfides with phenyliodine(III) bis(trifluoroacetate) (PIFA).[9] We report here an interrupted Pummerer-type reaction of sulfides using PIFA has been applied to prepare *N*-substituted isothiazol-3(2*H*)-ones via intramolecular N-S bond formation.

RESULTS AND DISCUSSION

The requisite amides (**4**) were readily prepared from (*Z*)-3-benzylsulfanylpropenoic acid (**3**) with Ph_3P/CCl_4-complex followed by treatment with appropriate amines.[10] Thus, treatment of **4** with PIFA containing trifluoroacetic acid (TFA) in CH_2Cl_2 caused cyclization to give *N*-substituted isothiazol-3(2*H*)-ones (**5**) in moderate yields. Under these conditions no sulfoxides or normal Pummerer-type products were obtained (Scheme II). The yields are summarized in Table 1.

Scheme II



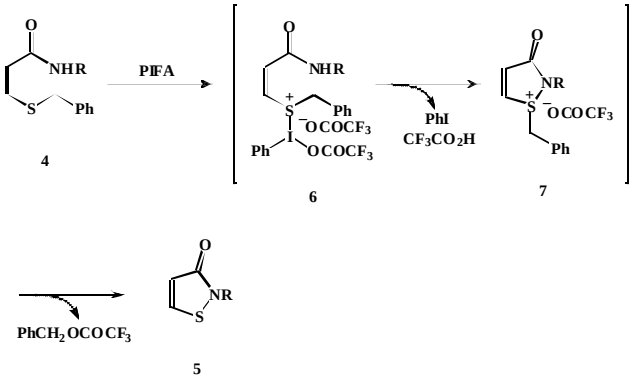
a) R = Pr^n **b)** R = Pr^i **c)** R = Bu^t **d)** R= Ph
e) R = 4-$MeOC_6H_4$ **f)** R= 4-ClC_6H_4

Table 1. Preparation of Amides **4** and *N*-Substituted Isothiazol-3(2*H*)-ones **5**

Product	R	Isolated Yield (%) **4**	**5**
a	Pr^n	70	71
b	Pr^i	72	65
c	Bu^t	71	67
d	Ph	75	72
e	4-$MeOC_6H_4$	74	65
f	4-ClC_6H_4	70	60

A mechanistic sequence for 1,2-benzisothiazol-3(2*H*)-one ring formation using PIFA is shown in Scheme III. The cyclization from **4** to **5** is assumed to proceed through interrupted Pummerer-type reaction intermediate (**7**) which would be formed by attack of PIFA on the sulfur atom of **4**, followed by simultaneous elimination of the iodobenzene and trifluoroacetic acid from the resultant sulfonium salt (**6**). Apparently, without the electron withdrawing group on the carbon alpha to the sulfide group, trifluoroacetate ion is not basic enough to generate the thionium ion.

Scheme III



4 6 7 5

In summary, our results herein demonstrate that the use of a combined reagent PIFA-TFA in CH_2Cl_2 is a convenient and useful method for the interrupted Pummerer-type reaction of sulfides to prepare *N*-substituted isothiazol-3(2*H*)-ones.

EXPERIMENTAL SECTION

All melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27 G spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini-200 or Varian Unity Plus 400 MHz. Chemical shifts were measured in ppm (δ) with respect to TMS. MS were obtained on a JEOL JMS D-300 instrument.

General Procedure for the Preparation of Amides 4a-4f

Triphenylphosphine (315 mg, 1.2 mmol) was added portionwise over 5 min to a solution of (*Z*)-3-benzylsulfanylpropenoic acid (**3**) (194 mg, 1 mmol), CCl_4 (308 mg, 2 mmol), and the requisite amine (2.1 mmol) in MeCN (25 mL). The resulting mixture was heated at 80 °C for 2 h. After removal of the solvent, the residue was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel with *n*-hexane:ethyl acetate (2:1) to give the products **4a-4f**.

(*Z*)-3-(Benzylsulfanyl)-*N*-propylpropenamide (4a)

Colorless needles; mp 107-108 °C (lit.,[7] 108-109 °C). IR (neat) υ: 3310, 1625, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (t, *J* = 7.6 Hz, 3H), 1.52 (tq, *J* = 7.6 and 7.2 Hz, 2H), 3.25 (dt, *J* = 7.2 and 5.6 Hz, 2H), 3.90 (s, 2H), 5.50 (br s, 1H), 5.71 (d, *J* = 10.0 Hz, 1H), 6.78 (d, *J* = 10.0 Hz, 1H), 7.30 (m, 5H); EI-MS *m/z* (relative intensity) 235 (M^+, 5), 144 (100), 91 (52), 65 (9).

(*Z*)-3-(Benzylsulfanyl)-*N*-isopropylpropenamide (4b)

Colorless needles; mp 120-122 °C (lit.,[7] 120-121 °C). IR (neat) υ: 3275, 1645, 1575, 1545 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.16 (d, *J* = 6.6 Hz, 6H), 3.91 (s, 2H), 4.13 (m, 1H), 5.66 (d, *J* = 9.9 Hz, 1H), 6.78 (d, *J* = 9.9 Hz, 1H), 7.24-7.36 (m, 5H); EI-MS *m/z* (relative intensity) 235 (M^+, 12), 144 (100), 102 (39), 91 (57), 65 (11).

(*Z*)-3-(Benzylsulfanyl)-*N*-tert-butylpropenamide (4c)

Colorless needles; mp 100-101 °C (lit.,[7] 99-100 °C). IR (neat) υ: 3300, 1635, 1575 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.37 (s, 9H), 3.90 (s, 2H), 5.21 (br s, 1H), 5.63 (d, *J* = 10.0 Hz, 1H), 6.74 (d, *J* = 10.0 Hz, 1H), 7.30 (m, 5H); EI-MS *m/z* (relative intensity) 249 (M^+, 3), 158 (90), 102 (100), 91 (66), 65 (9).

(*Z*)-3-(Benzylsulfanyl)-*N*-phenylpropenamide (4d)

Colorless needles; mp 166-167 °C (lit.,[7] 167-169 °C). IR (neat) υ: 3225, 1635, 1590, 1565 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.95 (s, 2H), 5.88 (d, *J* = 10.0 Hz, 1H), 6.98 (d, *J* = 10.0 Hz, 1H), 7.06-7.37 (m, 8H), 7.18 (br s, 1H), 7.56 (m, 2H); EI-MS *m/z* (relative intensity) 269 (M^+, 5), 178 (80), 93

(44), 91 (100), 65 (15).

(*Z*)-3-(Benzylsulfanyl)-*N*-(4-methoxyphenyl)propenamide (4e)

Colorless needles; mp 110-112 °C (lit.,[7] 111-112 °C). IR (neat) υ: 3275, 1635, 1565, 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 3.78 (s, 3H), 3.95 (s, 2H), 5.84 (d, *J* = 10.0 Hz, 1H), 6.83 (m, 2H), 6.95 (d, *J* = 10.0 Hz, 1H), 7.04 (br s, 1H), 7.25-7.35 (m, 7H), 7.47 (m, 2H); EI-MS *m/z* (relative intensity) 299 (M^+, 2), 208 (26), 123 (100), 91 (80).

(*Z*)-3-(Benzylsulfanyl)-*N*-(4-chlorophenyl)propenamide (4f)

Colorless needles; mp 129-130 °C. IR (neat) υ: 3375, 1650, 1565, 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.96 (s, 2H), 5.85 (d, *J* = 10.0 Hz, 1H), 7.02 (d, *J* = 10.0 Hz, 1H), 7.09 (br s, 1H), 7.22-7.36 (m, 7H), 7.52 (m, 2H); EI-MS *m/z* (relative intensity) 303 (M^+, 2), 212 (18), 177 (31), 127 (26), 91 (100), 65 (10). Anal. Calcd. for $C_{16}H_{14}ClNOS$: C, 4.60; H, 63.30; N, 4.60. Found: C, 4.59; H, 63.17; N, 4.61.

***N*-propylisothiazole-3(2*H*)-ones (5a)**

A solution of (*Z*)-3-(benzylsulfanyl)-*N*-propylpropenamide (**4a**) (235 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of the mixture of PIFA (538 mg, 1.25 mmol) and TFA (228 mg, 2 mmol) in CH_2Cl_2 at 0 °C and the mixture was stirred at the same temperature for 1 h. Then the mixture was refluxed for 2 h to complete the reaction. The resultant mixture was quenched with water and extracted with CH_2Cl_2. The mixture was dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by chromatography on a silica gel column, eluting with ethyl acetate to give 102 mg (71%) of **5a** as an oil. IR (neat) υ: 3100, 1620, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.97 (t, *J* = 7.6 Hz, 3H), 1.75 (dt, *J* = 7.6 and 7.2 Hz, 2H), 3.76 (t, *J* = 7.2 Hz, 2H), 6.28 (d, *J* = 6.4 Hz, 1H), 8.06 (d, *J* = 6.4 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 11.0, 23.1, 45.4, 114.7, 138.5, 168.9; EI-MS *m/z* (relative intensity) 143 (M^+, 44), 114 (27), 101 (100), 87 (23), 58 (14). HRMS *m/z* Calcd for C_6H_9NOS: 143.0404. Found: 143.0404.

***N*-Isopropylisothiazol-3(2*H*)-one (5b)**

By using a procedure similar to that described for **5a**, **4b** gave **5b** (65%) as an oil. IR (neat) υ: 2970, 1620, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.38 (d, *J* = 6.8 Hz, 6H), 4.80 (m, 1H), 6.26 (d, *J* = 6.4 Hz, 1H), 8.04 (d, *J* = 6.4 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 22.5, 46.1, 115.2, 138.4, 168.5; EI-MS *m/z* (relative intensity) 143 (M^+, 33), 101 (100), 87 (9), 73 (12), 58 (10). HRMS *m/z* Calcd for C_6H_9NOS: 143.0404. Found: 143.0404.

***N*-tert-Butylisothiazol-3(2*H*)-one (5c)**

By using a procedure similar to that described for **5a**, **4c** gave **5c** (67%); mp 84-85 °C (lit.,[5] 85-86 °C). IR (neat) υ: 2960, 2920, 1725, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.36 (s, 9H), 6.20 (d, *J* = 6.3 Hz, 1H), 7.92 (d, *J* = 6.3 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 28.9, 58.6, 128.7, 130.8, 167.7; EI-MS *m/z* (relative intensity) 157 (M^+, 40), 102 (100), 73 (7), 57 (33).

***N*-Phenylisothiazol-3(*2H*)-one (5d)**

By using a procedure similar to that described for **5a**, **4d** gave **5d** (72%); mp 91-92 °C (lit.,[5] 91-92 °C). IR (neat) υ: 3255, 3080, 1640, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 6.34 (d, *J* = 6.4Hz, 1H), 7.33-7.60 (m, 5H), 8.17 (d, *J* = 6.4 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 120.2, 124.3, 129.3, 129.7, 130.2, 144.0, 167.7; EI-MS *m/z* (relative intensity) 177 (M^+, 100), 104 (21), 77 (16), 58 (8).

***N*-(4-Methoxyphenyl)isothiazol-3(2*H*)-one (5e)**

By using a procedure similar to that described for **5a**, **4e** gave **5e** (65%); mp 92-93 °C (lit.,[7] 92-93 °C). IR (neat) υ: 3070, 1645, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 3.83 (s, 3H), 6.33 (d, *J* = 6.4 Hz, 1H), 6.97 (m, 2H), 7.44 (m, 2H), 8.15 (d, *J* = 6.4 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 55.5, 114.5, 114.6, 126.9, 128.9, 139.3, 159.0, 167.8; EI-MS *m/z* (relative intensity) 207 (M^+, 100), 192 (25), 164 (21), 134 (38), 121 (21), 106 (16).

***N*-(4-Chlorophenyl)isothiazol-3(2*H*)-one (5f)**

By using a procedure similar to that described for **5a**, **4f** gave **5f** (60%); mp 141-142 °C (lit.,[5] 142-144 °C). IR (neat) υ: 3070, 1640, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.34 (d, *J* = 6.4 Hz, 1H), 7.42 (m, 2H), 7.56 (m, 2H), 8.15 (d, *J* = 6.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 114.9, 125.7, 129.4, 132.9, 135.0, 139.5, 167.4; EI-MS *m/z* (relative intensity) 211 (M^+, 100), 148 (40), 138 (32), 111 (12), 90 (16), 58 (11).

ACKNOWLEDGEMENT

We gratefully acknowledge the National Science Council for financial support of this work (Grant No. NSC 89-2113-M-037-018).

Received May 29, 2001.

Key Words

Pummerer reaction; Thionium ion; Phenyliodine(III) bis(trifluoroacetate).

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