Efficient Fluoride-Mediated Synthesis of 5-Amino-Substituted Isothiazoles

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Received 13 March 2009; revised 18 March 2009

SYNTHESIS 2009, No. 14, pp 2361–2364
Advanced online publication: 25.05.2009
DOI: 10.1055/s-0029-1216844; Art ID: Z03909SS
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Abstract: Fluoride-mediated nucleophilic substitution reactions of tert-butyl 4,5-dichloroisothiazole-3-carboxylate with various amines occur under mild conditions yielding 5-(alkylamino)isothiazoles in moderate to high yields.

Key words: isothiazole, fluoride, substitution, amine

Isothiazole chemistry has been of great interest over past decades because of the large number of isothiazole compounds synthesized that have antibacterial, antiviral, antibiotic, or anticancer activity.1–3

Recently we have reported on the reaction of 4,5-dichloro-3-(trichloromethyl)isothiazole (1) with cyclic amines in aprotic solvent.4 Substitution of the chlorine atom at C5 of the isothiazole with cyclic amines proceeded at ambient temperature to give the corresponding 5-amino-4-chloro-3-(trichloromethyl)isothiazoles; other amines did not react under these conditions. Prolonged heating of substituted 4,5-dichloroisothiazole-3-carboxamides with an excess of amine gave the corresponding 5-alkylamino derivatives in low yields.5

Fluoride-mediated reactions are commonly used in SN2 and SNAr processes with O-, N-, and S-nucleophiles.6–8 However, the reaction of amines with isothiazole 1 in the presence of alkali metal fluoride does not give the expected result in aprotic solvents, as we have already established. At ambient temperature the reaction did not proceed, whereas increasing the temperature up to 60–70 °C led to a mixture of products, probably due to decomposition of the trichloromethyl group.

We decided to transform the trichloromethyl group into a tert-butyl carboxylate fragment, which is quite resistant to nucleophiles. tert-Butyl 4,5-dichloroisothiazole-3-carboxylate (2) was prepared from 4,5-dichloro-3-(trichloromethyl)isothiazole (1) according to literature procedures (Scheme 1).9 We used different experimental procedures to study chlorine substitution at C5 of the isothiazole ring (Table 1).

Initially we explored reactions of ester 2 with secondary cyclic amines. Piperidine and pyrrolidine reacted with 2 at room temperature in dimethyl sulfoxide or N,N-dimethyl-

Table 1 Nucleophilic Substitution of the Chlorine Atom at C5 in the Isothiazole Ring of 2a

<table>
<thead>
<tr>
<th>Product</th>
<th>NR1R2</th>
<th>Method</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>piperidin-1-yl</td>
<td>A</td>
<td>95</td>
</tr>
<tr>
<td>3b</td>
<td>pyrrolidin-1-yl</td>
<td>A</td>
<td>95</td>
</tr>
<tr>
<td>3c</td>
<td>morpholin-4-yl</td>
<td>A</td>
<td>90</td>
</tr>
<tr>
<td>3d</td>
<td>piperazin-1-yl</td>
<td>A</td>
<td>90</td>
</tr>
<tr>
<td>3e</td>
<td>NHBN</td>
<td>B</td>
<td>80</td>
</tr>
<tr>
<td>3f</td>
<td>NH(CH2)3Me</td>
<td>B</td>
<td>55</td>
</tr>
<tr>
<td>3g</td>
<td>NHi-Pr</td>
<td>B</td>
<td>55</td>
</tr>
<tr>
<td>3h</td>
<td>NHi-Bu</td>
<td>B</td>
<td>60</td>
</tr>
<tr>
<td>3i</td>
<td>N(Me)BN</td>
<td>B</td>
<td>35</td>
</tr>
<tr>
<td>3j</td>
<td>N(Me)Bu</td>
<td>B</td>
<td>30</td>
</tr>
<tr>
<td>3k</td>
<td>NBu2</td>
<td>B</td>
<td>15</td>
</tr>
</tbody>
</table>

a Conditions: A: DMSO (or DMF), 25–80 °C; B: KF, DMSO, 80 °C; C: CsF, DMSO, 60 °C; D: KF, NMP, 80 °C.

b Isolated yields.
c Determined by GC-MS analysis.

Scheme 1 Preparation of tert-butyl 4,5-dichloroisothiazole-3-carboxylate (2)
formamide to provide 5-(alkylamino) derivatives 3a,b in greater than 90% yield. Whereas piperazine and morpholine reacted only when heated (Method A) to give 5-(alkylamino) derivatives 3c,d; for other primary and secondary amines (benzylamine, hexan-1-amine, isopropylamine, tert-butylamine, N-methylbutan-1-amine, N-benzylmethylamine, and dibutylamine) the reaction mixture has to be heated up to 80 °C in the presence of six equivalents of solid alkali metal fluoride. When N,N-dimethylformamide was used, the product was contaminated with the 5-(dimethylamino) derivative formed from N,N-dimethylformamide decomposition products. The substitution of the chloride atom with primary amines proceeded in the presence of potassium fluoride at 80 °C to give 3e–h in 55–80% yields (Method B). However, N-methylalkylamine and dialkylamine derivatives 3i–k were obtained in low to moderate yields (15–35%). Replacing potassium fluoride with the more soluble cesium fluoride led to an increase in the product yield using both primary and secondary amines (Method C), but the temperature had to be reduced to 60 °C because of blackening of the mixture. With the aim of achieving higher product yields with potassium fluoride than those available, we replaced dimethyl sulfoxide with N-methylpyrrolidin-2-one (Method D). This provided an increase in yields of compounds 3e–k up to 70–80%; this is probably due to the improved solubility of potassium fluoride in N-methylpyrrolidin-2-one compared to dimethyl sulfoxide. In our experiments we used three equivalents of the corresponding amine, but we used six equivalents of isopropylamine to take account of its volatility. Disopropylamine did not react with ester 2 under any of the conditions utilized.

In conclusion, it was shown that amines substitute the chlorine atom at C5 in 4,5-dichloroisothiazole-3-carboxylate regioselectively, with no corresponding amide formation. It was observed that the amine activity decreases as shown in Scheme 2.

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\text{Scheme 2 Relative amine activity in nucleophilic aromatic substitution}
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Considering firstly the similar yields of products for primary alkylamines and the more basic N-methylalkylamines and secondly the dramatically decrease in yield for dibutylamine, we suggested that amine activity depends on the availability of the nitrogen atom.

All amines were purchased from Aldrich and used without further purification. DMF was dried by distillation over P2O5. DMSO and NMP was dried by distillation over CaH2. Alkali metal fluorides were heated at 200 °C in vacuo for 2 h prior to use. Melting points were determined on Boetius heating table. IR spectra was recorded on a Nicolet Protege spectrophotometer, using KBr discs. NMR spectra were recorded on a Bruker Avance-500 spectrometer in CDCl3 at 500 MHz for 1H NMR and 125 MHz for 13C NMR. GC-MS analysis were performed on a Hewlett Packard 5890/5972 spectrometer.

tert-Butyl 4,5-Dichloroisothiazole-3-carboxylate (2)
In a flask were placed anhyd t-BuOH (3.76 g, 50.8 mmol) and pyridine (4.02 g, 50.8 mmol) in anhyd Et2O (30 mL). 4,5-Dichloroisothiazole-3-carbonyl chloride (10 g, 46 mmol) in anhyd Et2O (60 mL) was added dropwise to the stirred soln. When the addition was complete, the mixture was stirred at r.t. for 4 h. The mixture was filtered and the precipitate was washed with Et2O (3 × 25 mL). The combined Et2O solns were washed with successive portions of 1 M H2SO4 until free of pyridine, then with 1 M Na2CO3 (2 × 20 mL), and dried (Na2CO3). After removal of the Et2O and distillation of the residue at reduced pressure (95–98 °C/1.33 mbar) the product 2 (9.1 g, 77%) was obtained.

5-(Alkylamino)- and 5-(Dialkylamino)-Substituted tert-Butyl 4-Chloroisothiazoles 3a–k; General Procedures

Method A: A soln of 2 (0.30 g, 1.18 mmol) and amine (3.54 mmol) in DMSO (3 mL) was stirred at 80 °C for 24 h; excess H2O (~30 mL) was added. The precipitate was filtered and dried.

Method B: A soln of 2 (0.30 g, 1.18 mmol), amine (3.54 mmol), and KF (0.40 g, 7.08 mmol) in DMSO (3 mL) was stirred at 80 °C for 12 h; excess H2O (~30 mL) was added. The aqueous layer was extracted with CH2Cl2 (3 × 30 mL) and the combined organic extracts were washed with brine (30 mL), dried (MgSO4), and concentrated in vacuo. The product was isolated by column chromatography (silica gel, hexane–EtOAc, 95:5).

Method C: A soln of 2 (0.30 g, 1.18 mmol), amine (3.54 mmol), and CsF (1.07 g, 7.08 mmol) in DMSO (3 mL) was stirred at 60 °C for 12 h; excess H2O (~30 mL) was added. The aqueous layer was extracted with CH2Cl2 (3 × 30 mL) and the combined organic extracts were washed with brine (30 mL), dried (MgSO4), and concentrated in vacuo. The product was isolated by column chromatography (silica gel, hexane–EtOAc, 95:5).

Method D: A soln of 2 (0.30 g, 1.18 mmol), amine (3.54 mmol), and KF (0.40 g, 7.08 mmol) in NMP (3 mL) was stirred at 80 °C for 12 h; excess H2O (~30 mL) was added. The aqueous layer was extracted with CH2Cl2 (3 × 30 mL) and the combined organic extracts were washed with brine (30 mL), dried (MgSO4), and concentrated in vacuo. The product was isolated by column chromatography (silica gel, hexane–EtOAc, 95:5).

tert-Butyl 4-Chloro-5-(pyrrolidin-1-yl)isothiazole-3-carboxylate (3a)
Mp 77–79 °C.
IR (KBr): 3007, 2972, 2937, 2850, 1725, 1519, 1410, 1367, 1245, 1158, 986, 855, 643 cm–1.

1H NMR: δ = 1.56 (m, 11 H), 1.7 (m, 4 H), 3.26 (t, J = 6.6 Hz, 4 H).

13C NMR: δ = 23.75, 25.25, 28.19, 52.21, 83.15, 107.94, 156.52, 159.98, 173.51.

GC-MS (EI, 70 eV): m/z = 302 [M]+, 246, 229, 84, 57.
Anal. Calcd for C13H16ClIN2O2S: C, 51.56; H, 6.32; Cl, 11.71; N, 9.25; S, 10.59. Found: C, 51.49; C, 6.41; Cl, 11.65; N, 9.20; S, 10.50.

tert-Butyl 4-Chloro-5-(pyrrolidin-1-yl)isothiazole-3-carboxylate (3b)
Mp 40–41 °C.
IR (KBr): 2977, 2931, 2881, 2849, 1719, 1548, 1429, 1246, 1159, 1004, 848, 638 cm–1.

1H NMR: δ = 1.56 (s, 9 H), 1.96 (t, J = 6.6 Hz, 4 H), 3.51 (t, J = 6.6 Hz, 4 H).

Anal. Calcd for C16H16ClN2O2S: C, 56.71; H, 5.65; Cl, 10.46; N, 8.29, 82.99, 102.68, 154.29, 159.60, 169.02.

-Butyl 4-Chloro-5-((morpholin-4-yl)isothiazole-3-carboxylate (3e)
Mp 78–90 °C.

IR (KBr): 3343, 2972, 2820, 2749, 1732, 1526, 1434, 1366, 1242, 1155, 1058, 989, 842, 807, 645 cm−1.

Anal. Calcd for C12H17ClN2O3S: C, 47.29; H, 5.62; Cl, 11.63; N, 9.17, 9.18; S, 10.52. Found: C, 47.15; C, 5.79; Cl, 11.58; N, 9.15; S, 10.47.

-Butyl 4-Chloro-5-(piperazin-1-yl)isothiazole-3-carboxylate (3d)
Mp 76–77 °C.


Anal. Calcd for C12H19ClN2O2S: C, 49.56; H, 6.59; Cl, 12.19; N, 9.63; S, 11.03. Found: C, 49.41; C, 5.79; Cl, 12.01; N, 11.09; S, 10.93.

References


