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

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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.

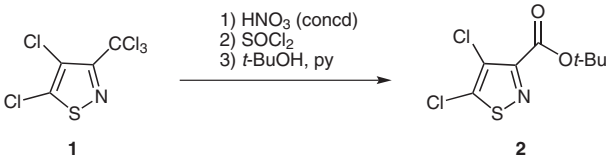
Key words: isothiazole, fluoride, substitution, amine

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 S_N2 and S_NAr 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).

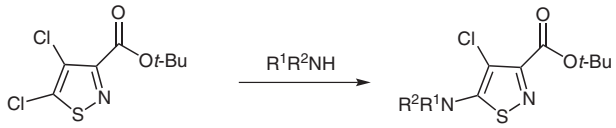


1 2

Scheme 1 Preparation of *tert*-butyl 4,5-dichloroisothiazole-3-carboxylate (**2**)

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 **2**[a]



2 3

Product	NR^1R^2	Method	Yield[b] (%)
3a	piperidin-1-yl	A	95
3b	pyrrolidin-1-yl	A	95
3c	morpholin-4-yl	A	90
		B	95
3d	piperazin-1-yl	A	90
		B	95
3e	NHBn	B	80
		C	87
		D	88
3f	$NH(CH_2)_5Me$	B	55
		C	76
		D	69
3g	NH*i*-Pr	B	55
		C	70
		D	75
3h	NH*t*-Bu	B	60
		C	89
		D	88
3i	N(Me)Bn	B	35
		C	74
		D	70
3j	N(Me)Bu	B	30
		C	75
		D	76
3k	NBu_2	B	15[c]
		C	15[c]
		D	30[c]

[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.

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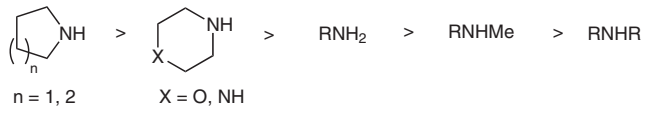
formamide to provide 5-(alkylamino) derivatives **3a**,**b** in greater than 90% yield. Whereas piperazine and morpholine reacted only when heated (Method A) to give 5-(alkylamino) derivatives **3c**,**d**; for other primary and secondary amines (benzylamine, hexan-1-amine, isopropylamine, *tert*-butylamine, *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 chlorine 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 compare 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. Diisopropylamine did not reacted 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.



Scheme 2 Relative amine activity in nucleophilic aromatic substitution

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 P_2O_5. DMSO and NMP was dried by distillation over CaH_2. 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 Protégé spectrophotometer, using KBr discs. NMR spectra were recorded on a Bruker Avance-500 spectrometer in $CDCl_3$ at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C 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 Et_2O (30 mL). 4,5-Dichloroisothiazole-3-carbonyl chloride (10 g, 46 mmol) in anhyd Et_2O (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 Et_2O (3 × 25 mL). The combined Et_2O solns were washed with successive portions of 1 M H_2SO_4 until free of pyridine, then with 1 M Na_2CO_3 (2 × 20 mL), and dried (Na_2CO_3). After removal of the Et_2O 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 H_2O (~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 H_2O (~30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), 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 H_2O (~30 mL) added. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), 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 H_2O (~30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The product was isolated by column chromatography (silica gel, hexane–EtOAc, 95:5).

tert-Butyl 4-Chloro-5-(piperidin-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}.

^{1}H NMR: δ = 1.56 (m, 11 H), 1.7 (m, 4 H), 3.26 (t, *J* = 4.8 Hz, 4 H).

^{13}C 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 $C_{13}H_{19}ClN_2O_2S$: 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}.

^{1}H 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).

^{13}C NMR: δ = 25.71, 28.19, 51.66, 82.91, 101.2, 156.2, 160.25, 168.07.

GC-MS (EI, 70 eV): *m*/*z* = 288 [M]$^+$, 232, 215, 70, 57.

Anal. Calcd for $C_{12}H_{17}ClN_2O_2S$: C, 49.91; H, 5.93; Cl, 12.28; N, 9.70; S, 11.10. Found: C, 49.85; C, 6.23; Cl, 12.11; N, 9.67; S, 11.06.

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

IR (KBr): 2991, 2972, 2937, 2858, 2828, 1716, 1508, 1411, 1366, 1274, 1237, 1156, 1116, 1050, 946, 888, 855, 647, 553 cm^{-1}.

^{1}H NMR: δ = 1.6 (s, 9 H), 3.31 (t, *J* = 4.7 Hz, 4 H), 3.85 (t, *J* = 4.7 Hz, 4 H).

^{13}C NMR: δ = 28.2, 50.92, 66.19, 83.45, 156.74, 159.71, 172.86.

GC-MS (EI, 70 eV): *m*/*z* = 304 [M]$^+$, 248, 231, 190, 57.

Anal. Calcd for $C_{12}H_{17}ClN_2O_3S$: C, 47.29; H, 5.62; Cl, 11.63; N, 9.19; S, 10.52. Found: C, 47.15; C, 5.79; Cl, 11.58; N, 9.15; S, 10.47.

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

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

^{1}H NMR: δ = 1.59 (s, 9 H), 1.84 (br s, 1 H), 3.96 (t, *J* = 4.9 Hz, 4 H), 3.28 (t, *J* = 4.9 Hz, 4 H).

^{13}C NMR: δ = 28.2, 45.42, 51.93, 83.32, 108.53, 156.67, 159.86, 173.21.

GC-MS (EI, 70 eV): *m*/*z* = 303 [M]$^+$, 205, 168, 56.

Anal. Calcd for $C_{12}H_{18}ClN_3O_2S$: C, 47.44; H, 5.97; Cl, 11.67; N, 13.83; S, 10.55. Found: C, 47.15; C, 6.13; Cl, 11.52; N, 13.88; S, 10.41.

***tert*-Butyl 5-(Benzylamino)-4-chloroisothiazole-3-carboxylate (3C)**
Mp 117–118 °C.

IR (KBr): 3199, 2973, 2930, 1725, 1555, 1422, 1351, 1243, 1158, 1092, 1064, 1007, 851, 743, 697 cm^{-1}.

^{1}H NMR: δ = 1.59 (s, 9 H), 4.39 (d, *J* = 5.5 Hz, 2 H), 5.45 (br s, 1 H), 7.34 (m, 5 H).

^{13}C NMR: δ = 28.22, 41.03, 51.47, 83.2, 103.54, 127.88, 128.5, 129.10, 135.93, 154.09, 159.62, 168.56.

GC-MS (EI, 70 eV): dec.

Anal. Calcd for $C_{15}H_{17}ClN_2O_2S$: C, 55.46; H, 5.28; Cl, 10.91; N, 8.62; S, 9.87. Found: C, 55.32; C, 5.68; Cl, 10.81; N, 8.64; S, 9.71.

***tert*-Butyl 4-Chloro-5-(hexylamino)isothiazole-3-carboxylate (3f)**
Mp 48–50 °C.

IR (KBr): 3279, 2978, 2950, 2928, 2855, 1719, 1560, 1420, 1369, 1235, 1157, 848 cm^{-1}.

^{1}H NMR: δ = 0.85 (t, *J* = 6.8 Hz, 3 H), 1.25–1.37 (m, 6 H), 1.56 (s, 9 H), 1.64 (q, *J* = 7.3 Hz, 2 H), 3.15 (m, 2 H), 4.9 (t, *J* = 5.3 Hz, 1 H).

^{13}C NMR: δ = 14.06, 22.59, 26.51, 28.18, 29.11, 31.44, 82.99, 102.68, 154.29, 159.60, 169.02.

GC-MS (EI, 70 eV): *m*/*z* = 318 [M]$^+$, 262, 191, 57.

Anal. Calcd for $C_{14}H_{23}ClN_2O_2S$: C, 52.73; H, 7.27; Cl, 11.12; N, 8.79; S, 10.06. Found: C, 52.63; C , 7.38; Cl, 11.06; N, 8.75; S, 9.93.

***tert*-Butyl 4-Chloro-5-(isopropylamino)isothiazole-3-carboxylate (3g)**
Mp 102–104 °C.

IR (KBr): 3288, 2975, 2932, 2870, 1720, 1553, 1423, 1397, 1368, 1255, 1158, 1013, 860, 841 cm^{-1}.

^{1}H NMR: δ = 1.27 (d, *J* = 6.3 Hz, 6 H), 1.56 (s, 9 H), 3.39 (oct, *J* = 6.5 Hz, 1 H), 4.73 (d, *J* = 7.4 Hz, 1 H).

^{13}C NMR: δ = 22.61, 28.2, 49.98, 83.01, 84.16, 102.87, 146.62, 154.16, 159.57, 167.65.

GC-MS (EI, 70 eV): *m*/*z* = 276 [M]$^+$, 220, 205, 178, 57, 43.

Anal. Calcd for $C_{11}H_{17}ClN_2O_2S$: C, 47.73; H, 6.19; Cl, 12.81; N, 10.12; S, 11.58. Found: C, 47.61; C, 6.25; Cl, 12.75; N, 10.09; S, 11.55.

***tert*-Butyl 5-(*tert*-Butylamino)-4-chloroisothiazole-3-carboxylate (3h)**
Mp 119–120 °C.

IR (KBr): 3288, 2974, 2927, 1723, 1539, 1417, 1367, 1254, 1222, 1157, 1012, 846, 644 cm^{-1}.

^{1}H NMR: δ = 1.36 (s, 9 H), 1.58 (s, 9 H), 4.85 (br s, 1 H).

^{13}C NMR: δ = 28.20, 28.69, 53.27, 83.06, 104.86, 153.17, 159.67, 165.10.

GC-MS (EI, 70 eV): *m*/*z* = 290 [M]$^+$, 234, 178, 57.

Anal. Calcd for $C_{12}H_{19}ClN_2O_2S$: C, 49.56; H, 6.59; Cl, 12.19; N, 9.63; S, 11.03. Found: C, 49.41; C, 6.70; Cl, 12.01; N, 9.59; S, 10.93.

***tert*-Butyl 5-[Benzyl(methyl)amino]-4-chloroisothiazole-3-carboxylate (3i)**
IR (film): 3029, 2979, 2931, 1727, 1537, 1453, 1410, 1393, 1368, 1247, 1158, 997, 851, 732, 698 cm^{-1}.

^{1}H NMR: δ = 1.59 (s, 9 H), 2.9 (s, 3 H), 4.6 (s, 2 H), 7.24–7.31 (m, 5 H).

^{13}C NMR: δ = 28.24, 41.02, 58.02, 83.15, 105.26, 128.04, 128.85, 136.12, 156.74, 160.08, 172.02.

GC-MS (EI, 70 eV): dec.

Anal. Calcd for $C_{16}H_{19}ClN_2O_2S$: C, 56.71; H, 5.65; Cl, 10.46; N, 8.27; S, 9.46. Found: C, 56.20; H, 5.74; Cl, 10.38; N, 8.25; S, 9.40.

***tert*-Butyl 5-[Butyl(methyl)amino]-4-chloroisothiazole-3-carboxylate (3j)**
IR (film): 2960, 2932, 2872, 1728, 1540, 1456, 1412, 1393, 1368, 1319, 1246, 1159, 1080, 1001, 990, 851, 771, 732 cm^{-1}.

^{1}H NMR: δ = 0.81 (s, 3 H), 1.22 (m, 2 H), 1.49 (m, 11 H), 2.94 (s, 3 H), 3.35 (m, 2 H).

^{13}C NMR: δ = 13.88, 19.86, 28.01, 29.38, 41.39, 54.71, 82.96, 103.25, 156.78, 160.18, 171.35.

GC-MS (EI, 70 eV): *m*/*z* = 304 [M]$^+$, 248, 231, 205, 57, 44.

Anal. Calcd for $C_{13}H_{21}ClN_2O_2S$: C, 51.22; H, 6.94; Cl, 11.63; N, 9.19; S, 10.52. Found: C, 51.01; H, 7.05; Cl, 11.59; N, 9.17; S, 10.48.

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