Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of 2-Substituted Benzothiazoles from 2-Fluorophenylisothiocyanate

Jeffrey J. Ares [a] [b]

[a] Department of Chemistry , Worcester Polytechnic Institute , Worcester, Massachusetts, 01609

[b] The Procter and Gamble Company, Miami Valley Laboratories , P.O. Box 398707, Cincinnati, OH, 45239-8707

Published online: 23 Sep 2006.

To cite this article: Jeffrey J. Ares (1991) Synthesis of 2-Substituted Benzothiazoles from 2-Fluorophenylisothiocyanate, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:5, 625-633, DOI: 10.1080/00397919108020829

To link to this article: http://dx.doi.org/10.1080/00397919108020829

SYNTHETIC COMMUNICATIONS, 21(5), 625-633 (1991)

SYNTHESIS OF 2-SUBSTITUTED BENZOTHIAZOLES FROM 2-FLUOROPHENYLISOTHIOCYANATE

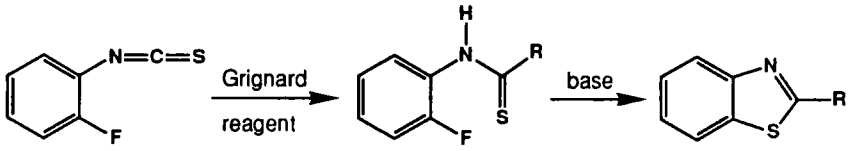
Jeffrey J. Ares*

Department of Chemistry
Worcester Polytechnic Institute
Worcester, Massachusetts 01609

ABSTRACT: Treatment of 2-fluorophenylisothiocyanate with a Grignard reagent, followed by base-induced cyclization of the resulting thioamide, provides a convenient method of synthesizing 2-substituted benzothiazoles. Best results are obtained upon isolation and purification of the intermediate thioamide, but a direct one-pot isothiocyanate-to-benzothiazole transformation has also been achieved.

Benzothiazoles are extremely important heterocycles from an industrial,[1] agricultural[2] and pharmaceutical[3] point of view. There are currently numerous methods available to synthesize benzothiazoles. By far the most common route involves condensation of 2-aminothiophenol with some form of a carboxylic acid derivative, including (but not limited to) acid chlorides and anhydrides,[1] selenoamides,[4] copper thiobenzoates,[5] imidates,[6] and carboxylic acids under acidic conditions.[7] In general, these reactions require reasonably harsh conditions, have some structural limitations, or proceed in only moder-

*Address correspondence to Jeffrey J. Ares, The Procter and Gamble Company, Miami Valley Laboratories, P.O. Box 398707, Cincinnati, OH 45239-8707



SCHEME 1

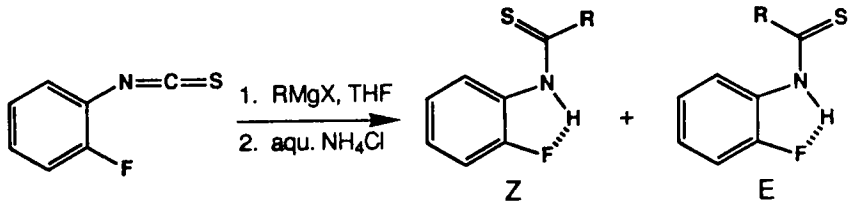
ate yield. Other methods of preparing benzothiazoles include thiocyanogenation of aryl amines[8] and cyclization of an arylthiourea.[9] These processes also have structural limitations, in all cases giving rise to 2-aminobenzothiazoles.

The synthesis of benzothiazoles via nucleophilic aromatic displacement reactions has been largely ignored. A report by Spitulnik[10] in 1976 describes the synthesis of 2-methylbenzothiazoles from 2-chloro or bromothioacetanilides by treatment with base in amide solvents at 150°C. We felt that 2-substituted benzothiazoles could be obtained from commercially available 2-fluorophenylisothiocyanate in a two-step process by first treating the isothiocyanate with a Grignard reagent, followed by a base-induced nucleophilic aromatic cyclization of the resulting thioamide (Scheme 1). In this report, we describe the successful realization of this objective, resulting in a mild high-yielding preparation of 2-substituted benzothiazoles.

2-Fluorophenylisothiocyanate was treated with a slight excess of Grignard reagents in tetrahydrofuran at 0°C and the results are indicated in Table 1. Thioamides 1a - 1d were obtained in good to excellent yields following purification by flash chromatography. In two instances, thioamide 1a (R = Me) and thioamide 1d (R = Bu), proton NMR spectroscopy of the purified product indicated the presence of two isomers. This phenomenon, originally noted for 1a by Walter and Sewekow in 1972,[11] was attributed to an intramolecular hydrogen bond between the thioamide proton and the fluorine

Table 1

Synthesis of Thioamides



Z E

Entry	R	X	Product	% Yield	Z:E Ratio[a]
1	Me	Br	1a	96	73:27
2	Ph	Br	1b	93	100:0
3	iPr	Cl	1c	79	100:0
4	Bu	Cl	1d	76	85:15

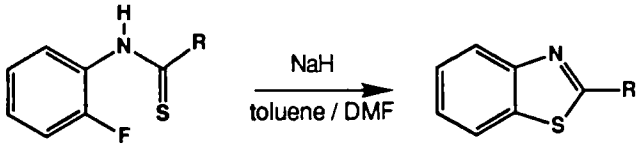
[a]Ratios determined by 200 MHz proton NMR spectroscopy.

atom, locking the thiocarbonyl and aromatic ring into a coplanar arrangement. The Z isomer predominates in all four cases, presumably due to the neutralizing effect of the thiocarbonyl and carbon-fluorine bond dipoles.[11] The presence of a reasonable amount of E isomer with the methyl thioamide and a small amount of E isomer with the butyl thioamide indicates that the steric effect of the substituent also plays a role in the product ratio.

The results of our thioamide cyclization experiments are collected in Table 2. Dissolution of the thioamide (or thioamide isomeric mixture) in toluene, followed by treatment with a slight excess of sodium hydride, warming, addition of dimethylformamide and heating for the indicated time period, resulted in generation of the desired benzothiazoles 2a - 2d in high yield following flash chromatographic purification.

Table 2

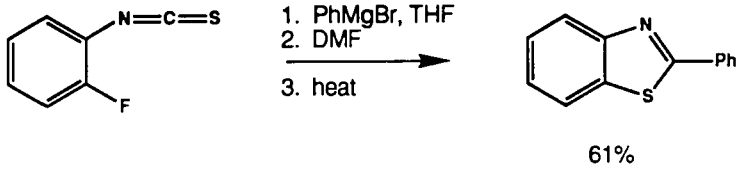
Synthesis of Benzothiazoles



Entry	R	Product	Reaction Time (hours)	% Yield
1	Me	2a	8	78
2	Ph	2b	2	91
3	iPr	2c	10.5	87
4	Bu	2d	7	90

We felt that since the thioamide formation requires a proton quench on an intermediate anionic species and since the thioamide is redeprotonated in the next step, it should be possible to effect the isothiocyanate-to-benzothiazole transformation in one reaction vessel. Such a one-pot transformation is indeed possible as indicated by the synthesis of 2-phenylbenzothiazole 2b in Scheme 2. Treatment of 2-fluorophenylisothiocyanate with phenyl magnesium bromide in tetrahydrofuran, followed by addition of dimethylformamide and heating, afforded 2b in 61% yield following chromatography and recrystallization. Therefore, although the direct one-pot transformation is successful in providing product, the two-step preparation is superior since the overall yield (84%) is significantly higher than that of the one-pot method.

In summary, commercially-available 2-fluorophenylisothiocyanate may be conveniently transformed into 2-substituted benzothiazoles by treatment with a Grignard reagent, followed by base-induced nucleophilic aromatic cycliza-



61%

SCHEME 2

tion of the resulting thioamides. The thioamides were found to exist predominantly or exclusively in the Z configuration. A direct one-pot isothiocyanate-to-benzothiazole conversion is also possible but proceeds in lower overall yield than the two-step transformation.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC200 spectrometer (200 MHz) in deuterochloroform with tetramethylsilane (TMS) as an internal reference. Data are reported as follows: chemical shift in ppm, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, quart = quartet, m = multiplet), integration, interpretation and coupling constants (Hz). Analytical thin-layer chromatography was performed on EM Science silica gel plates with F-254 indicator. Visualization was accomplished with UV light and iodine. Flash chromatography was performed by the method of Still.[12] Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Grignard reagents were purchased from Aldrich Chemicals and used as received. All reactions were run under an atmosphere of nitrogen.

Synthesis of Thioamides from 2-Fluorophenylisothiocyanate and a Grignard Reagent (Representative Procedure).

N-(2-fluorophenyl)-2-methylpropanethioamide (1c).

To 2-fluorophenylisothiocyanate (0.765 g, 0.617 mL, 5 mmol) in THF (12 mL) was added isopropyl magnesium chloride in ether (3 mL, 2 M solution, 6 mmol) *via* syringe at 0°C. The reaction mixture was stirred at 0°C for 2 h and then treated with a saturated solution of aqueous ammonium chloride (25 mL). The mixture was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were washed with water, brine, dried (Na_2SO_4) and evaporated. The resulting oil was purified by flash chromatography using hexane-ethyl acetate (8:1) to provide 1c as a yellow oil, 0.755 g (79%). ^1H NMR ($CDCl_3$/TMS) δ 8.68 (br s, 1H, N-H), 8.43 (m, 1H, aromatic H-C(6)), 7.22-7.07 (m, 3H, aromatic), 3.12-2.93 (m, 1H, H-C-C=S), 1.35 (d, 6H, CH_3, J = 8 Hz).

N-(2-fluorophenyl)ethanethioamide (1a): oil (mixture of isomers). ^1H NMR ($CDCl_3$/TMS, major isomer) δ 8.95 (br s, 1H, N-H), 8.24 (m, 1H, aromatic H-C(6)), 7.38-7.08 (m, 3H, aromatic), 2.71 (s, 3H, CH_3). This compound has previously been reported to have a mp of 45-46°C.[11]

N-(2-fluorophenyl)phenylmethanethioamide (1b): mp 73-74°C (lit[13] mp 77-78°C). ^1H NMR ($CDCl_3$/TMS) δ 9.10 (br s, 1H, N-H, exchangable with D_2O), 8.56 (br s, 1H, aromatic H-C(6)), 7.83 (d, 2H, aromatic H ortho to thiocarbonyl, J = 9 Hz), 7.56-7.33 (m, 3H), 7.30-7.10 (m, 3H).

N-(2-fluorophenyl)pentanethioamide (1d): oil (mixture of isomers). ^1H NMR ($CDCl_3$/TMS, major isomer) δ 8.86 (br s, 1H, N-H), 8.20 (m, 1H,

aromatic H-C(6)), 7.23-7.05 (m, 3H, aromatic), 2.80 (t, 2H, CH_2, J = 8 Hz), 1.92-1.71 (m, 2H, CH_2), 1.51-1.30 (m, 2H, CH_2), 0.94 (t, 3H, CH_3, J = 7.2 Hz).

Synthesis of Benzothiazoles from 2-Fluorophenylalkylthioamides (Representative Procedure).

2-(1-methylethyl)benzothiazole (2c).

To thioamide 1c (0.394 g, 2 mmol) in toluene (12 mL) was added sodium hydride (0.058 g, 2.4 mmol) with ice bath cooling. The mixture was stirred in an ice bath for 10 minutes and at room temperature for 30 minutes. The reaction mixture was then heated to reflux for 30 minutes and to the hot suspension was added dimethylformamide (DMF) (2 mL). The resulting solution was then heated and stirred at reflux for the indicated time period (10.5 h, Table 2), cooled, and poured into water (20 mL). The mixture was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were washed with water, brine, dried (Na_2SO_4) and evaporated. The resulting oil was purified by flash chromatography using hexane-ethyl acetate (12:1) to afford benzothiazole 2c as a clear oil, 0.308 g (87%). ^{1}H NMR ($CDCl_3$/TMS) δ 7.98 (d, 1H, aromatic, J = 10 Hz), 7.82 (d, 1H, aromatic, J = 10 Hz), 7.49-7.28 (m, 2H, aromatic), 3.52-3.31 (m, 1H, H-C-C=N), 1.47 (d, 6H, CH_3, J = 7 Hz). This spectrum is analogous to that previously recorded for this compound in carbon tetrachloride.[14]

2-methylbenzothiazole 2a: oil. δ 7.94 (d, 1H, aromatic, J = 8 Hz), 7.80 (d, 1H, aromatic, J = 8 Hz), 7.48-7.27 (m, 2H, aromatic), 2.81 (s, 3H, CH_3). This spectrum is in agreement with that obtained from an authentic sample (Aldrich Chemicals).

2-butylbenzothiazole (2d): oil. δ 7.97 (d, 1H, aromatic, J = 8 Hz), 7.82 (d, 1H, aromatic, J = 8 Hz), 7.47-7.28 (m, 2H, aromatic), 3.11 (t, 2H, CH_2, J = 7 Hz), 1.94-1.78 (m, 2H, CH_2), 1.52-1.37 (m, 2H, CH_2), 0.96 (t, 3H, CH_3, J = 6 Hz). This spectrum is analogous to that previously recorded for this compound in carbon tetrachloride.[14]

One Pot Synthesis of 2-Phenylbenzothiazole (2b) from 2-Fluorophenylisothiocyanate.

To 2-fluorophenylisothiocyanate (0.612 g, 0.494 mL, 4 mmol) in THF (10 mL) was added phenyl magnesium bromide in ether (1.6 mL, 3M solution, 4.8 mmol) via syringe at 0°C. The reaction mixture was stirred at 0°C for 2 h, warmed to room temperature, and heated to reflux for 3 h. TLC analysis at this time using hexane-ethyl acetate (4:1) indicated consumption of starting material. DMF (2 mL) was added, and the reaction mixture was heated to reflux for 20 h. Additional DMF was added (3 mL), and the reaction mixture was stirred at reflux for an additional 3 h and at room temperature for 48 h. The resulting dark suspension was poured into 1N HCl (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and evaporated. The resulting oil was purified by flash chromatography using hexane-ethyl acetate (8:1) to afford 2b as a yellow solid (0.653 g). Recrystallization from ethanol provided 2b as pale yellow needles, 0.514 g (61%). mp 112-114°C (lit[5] mp 115- 116°C). ^{1}H NMR ($CDCl_3$/TMS) δ 8.15-8.04 (m, 3H), 7.89 (d, 1H, J = 8 Hz), 7.56-7.34 (m, 5H). This spectrum is consistent with that previously reported.[5]

Acknowledgements: The author wishes to thank the Worcester Polytechnic Institute Research Development Council for financial support, Professor

David Todd for helpful discussions, and Mary Ballard and Susan Wade for typing this manuscript.

References

1. Harmer, F. M., in "The Chemistry of Heterocyclic Compounds," Ed., Weissberger, A., Volume 18, Interscience, New York, 1964; Chapter 6.

2. Hisano, T., Ichikawa, M., Tsumoto, K., Tasaki, M., Chem. Pharm. Bull., 1982, 30, 2996.

3. Wattenberg, L. W., Page, M. A., Leong, J. L., Cancer Res., 1968, 28, 2539.

4. Cohen, V. I., J. Heterocycl. Chem., 1979, 16, 13.

5. Osuka, A., Uno, Y., Horiuchi, H., Suzuki, H., Synthesis, 1984, 145.

6. McKillop, A., Henderson, A. Ray, P. S., Avendano, D., Molinero, E. G., Tetrahedron Lett., 1982, 23, 3357.

7. Boger, D. L., J. Org. Chem., 1978, 43, 2296.

8. Lin, A. J., Kasina, S., J. Heterocycl. Chem., 1981, 18, 759.

9. Patil, D. G., Chedekel, M. R., J. Org. Chem., 1984, 49, 997.

10. Spitulnik, M. J., Synthesis, 1976, 730.

11. Walter, W., Sewekow, U., Liebigs Ann. Chem., 1972, 761, 104.

12. Still, W. C., Kahn, M., Mitra, A. J., J. Org. Chem., 1978, 43, 2923.

13. Roe, A., Tucker, W. P., J. Heterocycl. Chem., 1965, 2, 148.

14. Cohen, V. I., Pourabass, S., J. Heterocycl. Chem., 1977, 14, 1321.

(Received in USA 4 January, 1991)