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Tetrahedron Letters 45 (2004) 9373–9375
Tetrahedron Letters

Synthesis of 2-*N*-alkyl(aryl)amino-7-nitrobenzothiazoles

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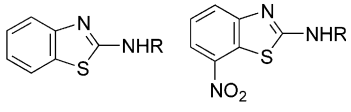
Received 22 August 2004; revised 20 October 2004; accepted 21 October 2004
Available online 5 November 2004

Abstract—A highly efficient synthesis of 2-*N*-alkyl(aryl)amino-7-nitrobenzothiazoles has been developed. The key step involves intramolecular cyclization of a thiourea facilitated by the nitro group.

In recent years, thousands of examples of the 2-*N*-alkyl(aryl)aminobenzothiazole scaffold (**1**) have been disclosed in the scientific and patent literature. Many of these compounds have interesting biological properties. Accordingly, this bicyclic ring system has become a popular building block in medicinal chemistry due to its crucial role in agents having anti-inflammatory, anti-microbial, anti-tumor, neuroprotective, and other therapeutically useful activities. For instance, *N*-substituted 2-aminobenzothiazoles were reported to be potent inhibitors of 5-lipoxygenase and thromboxane A_2 synthetase.[1] In addition, 2-aminobenzothiazole analogues having anti-bacterial and anti-fungal activities have been described by several groups.[2] Others have reported the potential neuroprotectant activity of 2-(piperazinoalkyl)aminobenzothiazoles having high affinity for dopaminergic D_4 receptors.[3] Recently, 2-aminobenzothiazoles were found to suppress the formation of insoluble polyglutamine-containing aggregates in neurons and therefore may represent attractive agents for the treatment of Huntington's disease and related conditions.[3] Moreover, 2-aminobenzothiazoles have been reported to be inhibitors of serine/threonine and tyrosine kinases such as those associated with fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and platelet derived growth factor (PDGF) receptors and hence are particularly important in hyperproliferative diseases such as cancer, psoriasis, and rheumatoid arthritis.[4]

Despite this attention, very few publications describing 7-nitro-2-aminobenzothiazoles have appeared and no efficient methodology has been disclosed for the synthesis of *N*-alkyl- or *N*-aryl-7-nitro derivatives (**2**). Conceptually, direct nitration of *N*-substituted 2-aminobenzothiazoles (**1**) would provide **2** but is likely to generate a mixture of regioisomers that would require separation. One literature account describes the preparation of 7-nitro-2-aminobenzothiazole (**2**, R = H) via bromine-mediated cyclization of *N*-(3-nitrophenyl)thiourea, but the methodology is not applicable to the synthesis of analogues where the *N*-substituent is susceptible to electrophilic bromination (i.e., methoxyphenyl).[5] In this communication, a facile and general method is described for the preparation of 2-*N*-alkyl-(aryl)amino-7-nitrobenzothiazoles (**2**) that is applicable to a broad variety of substituents on the amine nitrogen.



1 **2**

Synthesis of the title compounds is shown in Scheme 1. The starting material is 3-nitro-2-chloroaniline (**4**), which can be generated in two steps from commercially available 2,6-dinitroaniline (**3**) in 54% yield.[6] Reaction of amino compound **4** with thiophosgene provides isothiocyanate **5** (98%). Treatment of isothiocyanate **5** with an alkyl- or aryl-substituted amine and potassium carbonate in isopropyl alcohol generates the corresponding thiourea **6** that is then cyclized in situ at reflux to provide the desired product **7**.[7] Under typical experimental

Keyword: 2-*N*-alkyl(aryl)amino-7-nitrobenzothiazole.
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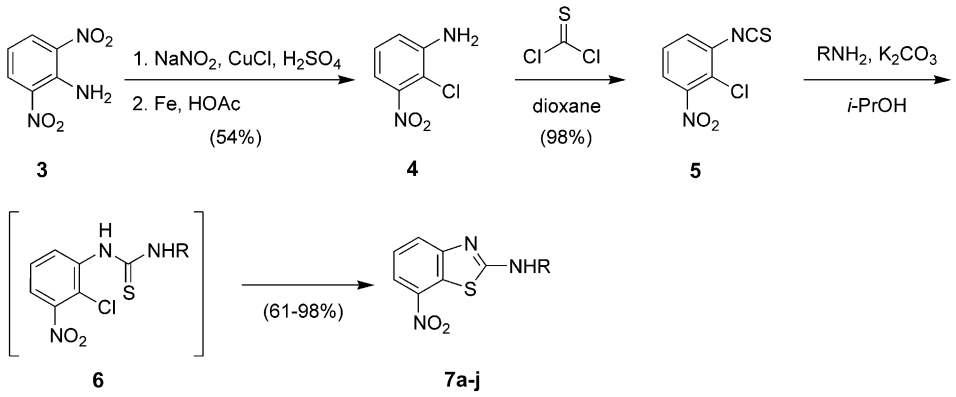
doi:10.1016/j.tetlet.2004.10.117



Scheme 1. Synthesis of 2-*N*-alkyl(aryl)amino-7-nitrobenzothiazoles via cyclization of *N*-(2-chloro-3-nitrophenyl)thioureas.

conditions, 1.0 equiv of 2-chloro-1-isothiocyanato-3-nitrobenzene (**5**) was dissolved in isopropanol, followed by the addition of 2.0 equiv of potassium carbonate and 1.0 equiv of the desired amine. The mixture was refluxed until the cyclization was complete, then filtered. The filtrate was concentrated and the residue was purified by flash chromatography. Using this methodology, numerous 2-amino-7-nitrobenzothiazoles (**7**) were synthesized as shown in Table 1. Yields for the two-step, one-pot sequence ranged from 61 to 98%. When aliphatic amines were used, the conversion of intermediate **5** to products **7** was fast and proceeded in high yields. When aromatic amines such as aniline or electron-rich 3,4,5-trimethoxyaniline were used, similar results were achieved. However, electron deficient aromatic amines required longer reaction times and resulted in comparatively lower yields.[8]

In summary, a highly efficient synthesis of 2-*N*-alkyl-(aryl)amino-7-nitrobenzothiazoles (**7**) was developed that generates the desired compounds in four steps and in moderate to high yields from commercially available starting materials. These nitro compounds represent versatile intermediates that may be useful in the synthesis of potent inhibitors of many drug targets. They can be further elaborated by reducing the nitro group to an amino group that may serve as an attachment point for various pharmacologically interesting substituents.

Table 1.

Entry	R	Product	Yield (%)[a]	Reaction time (h)
1	Methyl	**7a**	98	3
2	*n*-Butyl	**7b**	94	3
3	Pyridin-2-yl	**7c**	61	5
4	Phenyl	**7d**	96	3
5	2,6-Dimethylphenyl	**7e**	94	3
6	Cyclopentyl	**7f**	96	3
7	Cyclohexyl	**7g**	98	3
8	3,4,5-Trimethoxyphenyl	**7h**	92	3
9	4-Chlorophenyl	**7i**	81	12
10	4-Chloro-2-fluorophenyl	**7j**	62	12

[a] Isolated yields from compound **5**, after purification by flash chromatography.

Acknowledgements

The authors thank Dr. Ignatius Turchi of J & JPRD for suggesting the benzothiazole scaffold and for many helpful discussions during the course of this work.

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8. Spectroscopic data for compounds in Table 1: *2-(N-Methyl)-amino-7-nitrobenzothiazole* (**7a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 8.1 Hz, 1H), 5.4 (br s, 1H), 3.19 (d, J = 3.6 Hz, 3H); ^{13}C NMR (100 MHz, THF): δ 168.28, 154.59, 140.71, 125,58, 124.07, 122.29, 114.65, 28.59; FTIR (neat, cm^{-1}): 2890, 1650, 1500; MS (ES) *m/z*: 210.2 (M+H$^+$).
2-(N-n-Butyl)amino-7-nitrobenzothiazole (**7b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (dd, J = 8.2 Hz, 0.9 Hz, 1H), 7.78 (dd, J = 8.0, 0.9 Hz, 1H), 7.78 (t, J = 8.1 Hz, 1H), 5.60 (br s, 1H), 3.50 (t, J = 7.1 Hz, 2H), 1.72 (p, J = 7.2 Hz, 2H), 1.50 (sextet, J = 7.6 Hz, 2H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, THF): δ 169.80, 156.78, 142.86, 127.67, 126.14, 124.38, 116.76, 44.85, 32.06, 20.65, 13.82; FTIR (neat, cm^{-1}): 2950, 2850, 2350, 1630, 1480; MS (ES) *m/z*: 252.1 (M+H$^+$).
2-(N-Pyridin-2-yl)amino-7-nitrobenzothiazole (**7c**): ^{1}H NMR (300 MHz, DMSO): δ 11.9 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.83 (t, J = 7.1 Hz, 1H), 7.65 (t, J = 7.0 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.09 (t, J = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO): 163.20, 152.20, 151.10, 146.90, 142.37, 138.89, 128.44, 126.62, 125.98, 118.38, 117.75, 118.38, 117.75, 111.78. FTIR (neat, cm^{-1}): 1600, 1520, 1400, 1290; MS (ES) *m/z*: 273.1 (M+H$^+$).
2-(N-Phenyl)amino-7-nitrobenzothiazole (**7d**): ^{1}H NMR (300 MHz, DMSO): δ 10.8 (s, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 2H), 7.53 (t, J = 8.1 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.03 (t, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO): δ 165.57, 155.66, 142.21, 141.93, 129.29, 126.94, 126.59, 124.42, 122.60, 119.35, 117.28; FTIR (neat, cm^{-1}): 2300, 1550, 1310; MS (ES) *m/z*: 272.2 (M+H$^+$).
2-(N-2,6-Dimethylphenyl)amino-7-nitrobenzothiazole (**7e**): ^{1}H NMR (400 MHz, DMSO): δ 10.0 (s, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.84 (d,J = 7.9 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.23 (s, 3H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, DMSO): δ 155.06, 141.61, 136.72, 135.86, 128.50, 127.59, 126.41, 124.35, 116.90, 17.86; FTIR (neat, cm^{-1}): 3490, 1600, 1250; MS (ES) *m/z*: 300.0 (M+H$^+$).
2-(N-Cyclopentyl)amino-7-nitrobenzothiazole (**7f**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.39 (t, J = 8.1 Hz, 1H), 7.18 (s, 1H), 4.14 (m, 1H), 2.14 (m, 2H), 1.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.25, 154.81, 141.98, 126.66, 125.95, 123.73, 116.81, 57.32, 33.13, 23.07; FTIR (neat, cm^{-1}): 3480, 1620, 1240; MS (ES) *m/z*: 264.1 (M+H$^+$).
2-(N-Cyclohexyl)amino-7-nitrobenzothiazole (**7g**): ^{1}H NMR (400 MHz, DMSO): δ 8.41 (d, J = 7.4 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 8.1 Hz, 1H), 3.77 (br s, 1H), 2.04 (m, 2H), 1.74 (m, 2H), 1.62 (m, 1H), 1.43-1.18 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.46, 155.28, 141.40, 126.49, 126.03, 123.51, 116.16, 54.83, 32.11, 25.15, 24.30; FTIR (neat, cm^{-1}): 3320, 2980, 1520, 1375; MS (ES) *m/z*: 278.1 (M+H$^+$).
2-(N-3,4,5-Trimethoxyphenyl)amino-7-nitrobenzothiazole (**7h**): ^{1}H NMR (400 MHz, DMSO): δ 10.73 (s, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 8.1 Hz, 1H), 7.16 (s, 2H), 3.84 (s, 6H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 164.25, 154.47, 152.97, 141.54, 136.01, 133.17, 126.43, 126.01, 125.17, 117.82, 96.37, 60.10, 55.75; FTIR (neat, cm^{-1}): 3450, 1510 cm^{-1}. MS (ES) *m/z*: 362.0 (M+H$^+$).
2-(N-4-Chlorophenyl)amino-7-nitrobenzothiazole (**7i**): ^{1}H NMR (400 MHz, DMSO): δ 10.93 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 7.9 Hz, 1H), 7.83 (d, J = 8.1 Hz, 2H), 7.60 (t, J = 7.8 Hz, 2H), 7.42 (d, 2H); ^{13}C NMR (100 MHz, DMSO): δ 164.04, 154.29, 141.65, 138.84, 128.92, 126.68, 126.22, 126.13, 125.41, 119.67, 118.22; FTIR (neat, cm^{-1}): 3470, 1600; MS (ES) *m/z*: 306.0 (M+H$^+$).
2-(N-4-Chloro-2-fluorophenyl)amino-7-nitrobenzothiazole (**7j**): ^{1}H NMR (400 MHz, DMSO): δ 10.75 (s, 1H), 8.59 (t, J = 8.8 Hz, 1H), 8.14 (d,J = 8.2 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.60 (t, J = 7.8 Hz, 2H), 7.54 (d, J = 11.1 Hz, 2H), 7.36 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO): 164.56, 153.74, 150.78, 141.62, 127.00, 126.90, 126.57, 125.63, 124.75, 122.17, 118.41, 116.06, 115.83; FTIR (neat, cm^{-1}): 3450, 1610; MS (ES) *m/z*: 324.0 (M+H$^+$).