A Simple, Mild, and Practical Method for the Esterification and Thioesterification of Anthranilic Acid Utilizing *N*-(2-Aminobenzoyl)benzotriazole

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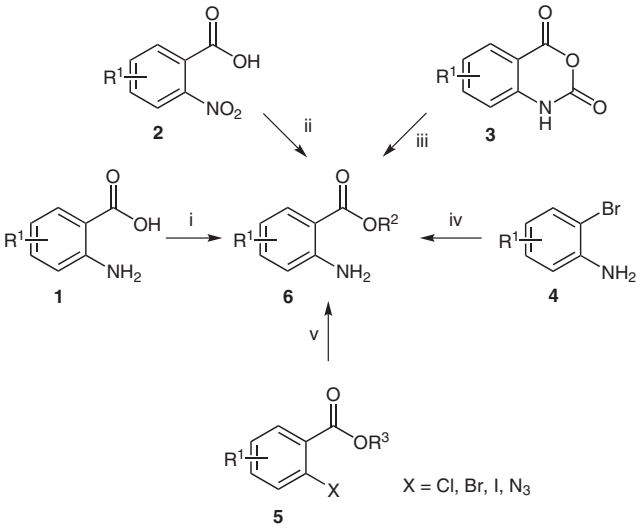
Received: 01.05.2013; Accepted after revision: 26.06.2013

Abstract: A convenient and efficient method for the preparation of anthranilic esters and anthranilic thioesters has been developed by the treatment of *N*-(2-aminobenzoyl)benzotriazoles with alcohols and thiols in the presence of 4-(dimethylamino)pyridine (DMAP).

Key words: alcohols, esterification, esters, heterocycles, thiols

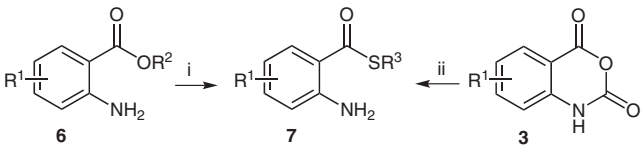
The synthesis of anthranilic acid derivatives is an important and useful task in organic chemistry owing to their importance in the preparation of nitrogen-containing heterocycles[1] with biologically or pharmacologically important activity, such as antitumor, antihypertensive, analgesic, or antibacterial activity. In addition to the use of anthranilic acid derivatives in the synthesis of heterocyclic compounds, some amide derivatives of anthranilic acid show biological activity[2] or they serve as starting materials for *o*-aminonitriles, which are versatile synthons for useful heterocycles.[3] Because of their powerful and pleasant scents and tastes, some anthranilic acid esters find more application in the fragrance and flavor industries.[4] Contributing to their industrial and synthetic importance, some ester derivatives of anthranilic acid also exhibit antibacterial and antifungal activity against microorganism[5] and some are effective as a repellent to prevent birds feeding on crops.[6] Glafenine, a useful anthranilic acid ester derivative, is used as an analgesic.[7] Like most anthranilic acid derivatives, thioester derivatives of anthranilic acid are also useful substrates for the cross coupling of organostannanes to give ketones,[8] for the protection of various thiols,[9] and for the preparation of symmetrical disulfides that have significant activity against human malignant cell lines including chemotherapy-resistant subclones, and they can serve as starting materials for the synthesis of various novel derivatives of quinolinone.[1c]

There are many studies that employed different routes and reagents to anthranilamides in the literature. However, most studies on the synthesis of anthranilic acid esters and thioesters are mainly based on the esterification of anthranilic acid or isatoic anhydride with an alcohol and thiol. Literature methods to anthranilic esters **6** include (Scheme 1): (i) the reaction of anthranilic acid **1** with alcohols in the presence of acid catalysts[4,5,10] or with an alkylating agent, like alkyl halides,[11a] dialkyl carbonate,[11b] diazomethane,[11c] polymer-supported triazine (PST),[11d] or dimethyl carbonate/diethyl carbonate;[11e] (ii) the reaction of 2-nitrobenzoic acid **2** with an alcohol, followed by catalytic reduction of the nitro group;[12] (iii) the reaction of isatoic anhydride **3** with alcohols;[13] (iv) the metal-catalyzed methoxycarbonylation of 2-bromoaniline **4**;[14] and (v) the reduction of *o*-halobenzoates[15a,b] **5** or the amination of *o*-azidobenzoates in the presence of various reagents.[15c]



Scheme 1 The preparation of anthranilic esters; for i–v see the discussion

Acetyl CoA is an important thioesters that appears in many biological processes.[16] Apart from their biological importance, thioesters have also widespread applications in synthetic organic chemistry for the preparation of numerous compounds. However, only two methods are reported for anthranilic thioesters **7** (Scheme 2): (i) the thermolysis of methyl anthranilate **6** with thiophenol;[17] and (ii) the reaction of isatoic anhydride **3** with various thiols.[8,9,13a]



Scheme 2 The preparation of anthranilic thioesters; for i and ii see the discussion

SYNTHESIS 2013, 45, 2551–2556
Advanced online publication: 19.07.2013
DOI: 10.1055/s-0033-1339469; Art ID: SS-2013-T0326-OP

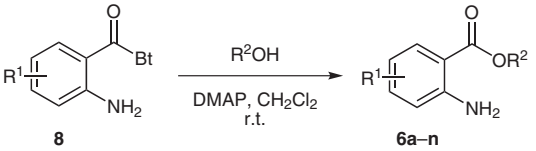
Esterification of anthranilic acid with an alcohol is often conducted under strongly acidic conditions. However, acid-catalyzed esterification of anthranilic acid is extremely difficult owing to the presence of the *ortho*-substituted amine functionality. Large amounts of acid are required to block the *ortho* position of anthranilic acid before it is esterified with an alcohol. Using acid in large amounts leads to disposal problems after the reaction.[4,5,10] Alkylating agents used in some methods for the synthesis of anthranilic esters are toxic and explosive;[11c] in addition, some are unstable at room temperature[11d] or are not sufficiently reactivity,[11e] hence high reaction temperatures and long reaction times are required. The reaction of isatoic anhydride with an alcohol is a well-known general method for the preparation of anthranilic esters and thioesters. However, this method commonly requires the handling of toxic reagents to prepare suitable isatoic anhydrides.[18] Steric hindrance and the nature and the activity of the nucleophile may also stimulate the formation of byproducts.[13a] There are few studies and a limited variety of substrates for the synthesis of anthranilic acid thioesters. The methods used in these studies mainly employed isatoic anhydrides. These literature procedures have some drawbacks like high temperatures,[8,13a,17] long reaction times,[9] or unsatisfactory yields.[17] In the light of these facts, there is still a need for more general methods and alternative active derivatives of anthranilic acid, capable of reacting with nucleophiles directly under mild conditions.

N-Acylbenzotriazoles are stable crystalline compounds and that are readily prepared in one step from carboxylic acids even in cases where an acid-sensitive functionality is present. They are of great importance in the synthesis of heterocycles[19a] and ketones,[19b] for the conversion of amines into amides,[19c,d] and for the acylation of alcohols and thiols to give esters[19e] and thioesters.[19e,f]

We have recently synthesized amide derivatives of anthranilic acid using *N*-acylbenzotriazoles in high yields.[20] We first prepared *N*-(2-aminobenzoyl)benzotriazoles by activation of anthranilic acid with benzotriazole using mild *N*,*N*′-dicyclohexylcarbodiimide coupling conditions and then treatment with ammonia or primary and secondary amines to synthesize anthranilic acid amides. In continuation of our previous work, we herein aimed to synthesize the ester and thioester derivatives of anthranilic acids.

Anthranilic acid esters **6a**–**n** were synthesized by the reaction of various alcohols with *N*-(2-aminobenzoyl)benzotriazoles **8** in the presence of 4-(dimethylamino)pyridine at room temperature (Table 1). Using this method, a wide variety of anthranilic acid esters with alkyl, aryl, ether, cycloalkyl, haloalkyl, and alkenyl moieties attached to the ester oxygen were synthesized under mild reaction conditions in high yields. The method worked well for all kinds of alcohols, except in the case of the synthesis of **6e** and **6m**. Due to the steric effect of the 6-methyl group, conversion into **6e** was achieved in only 55% yield. The alcohol used in the synthesis of **6m** has an active carbon attached to bromide. Therefore, the attack of the free amino group of anthranilic acid at this active center was considered as the cause of the low yield of **6m** (24%).

Table 1 Preparation of Anthranilic Acid Esters **6a**–**n**



8 **6a–n**

Entry	Product	R^1	R^2	Yield (%)
1	**6a**	H	Ph	80 (92)[a]
2	**6b**	3-Me	4-$MeOC_6H_4$	91
3	**6c**	4-Me	CH_2CH_2OEt	67
4	**6d**	5-Me	Ph	78 (91)[a]
5	**6e**	6-Me	cyclopentyl	55
6	**6f**	5-OMe	Cy	94
7	**6g**	4-Cl	*i*-Pr	84
8	**6h**	5-Cl	Pr	97
9	**6i**	5-Br	$(CH_2)_3Ph$	98
10	**6j**	5-I	4-ClC_6H_4	97
11	**6k**	3,5-Cl_2	Pr	92
12	**6l**	3,5-Br_2	$(CH_2)_4Me$	88
13	**6m**	4,5-$(OMe)_2$	CH_2CH_2Br	24
14	**6n**	3,4,5-$(OMe)_3$	$(CH_2)_3CH=CH_2$	90

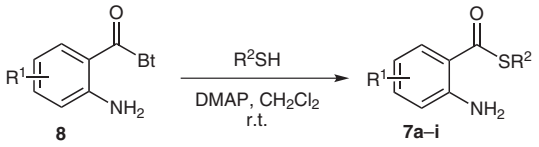
[a] Reported yields.[13b]

The structure of anthranilic acid esters **6a**–**n** was proven by various spectroscopic methods. The disappearance of the signals observed at δ = 8.37–8.17 as doublets and at δ = 7.69–7.55 as triplets in ^1H NMR indicated the loss of the benzotriazolyl group during the reaction. The ^{13}C NMR spectra of compounds clearly showed a signal at δ = 166.3–167.9 corresponding to the ester carbonyl groups of the products. Moreover, mass and IR spectral data were also in accordance with the proposed structures.

Treatment of *N*-(2-aminobenzoyl)benzotriazoles **8** with various thiols bearing alkyl, aryl, thiol, and ester moieties resulted in the formation of anthranilic acid thioesters **7a**–**i** with different structural features. The reactions proceeded in dichloromethane with 4-(dimethylamino)pyridine as the catalyst at room temperature. Anthranilic acid thioesters were successfully synthesized in high yields (Table 2). NMR spectral data supported the structural assignments of anthranilic acid thioesters. In addition to the absence of benzotriazole signals observed by ^1H and ^{13}C NMR, ^{13}C NMR spectra of the products **7a**–**i** revealed a characteristic signal in the region δ = 189.8–196.7, which corresponds to the thioester carbonyl carbon. Data ob-

tained from mass spectrometry and IR spectroscopy were compatible with the NMR results.

Table 2 Preparation of Anthranilic Acid Thioesters **7a–i**



Entry	Product	R^1	R^2	Yield (%)
1	**7a**	H	CH_2CH_2SH	80
2	**7b**	3-Me	Ph	85
3	**7c**	3-Me	CH_2CO_2Et	100
4	**7d**	4-Me	Ph	97
5	**7e**	5-Me	CH_2CH_2SH	71
6	**7f**	4,5-$(OMe)_2$	CH_2CO_2Et	90
7	**7g**	4-Cl	CH_2CO_2Et	91
8	**7h**	5-Br	Ph	92
9	**7i**	5-I	Et	96

In conclusion, we have used a new and general method to prepare a series of anthranilic acid esters and thioesters with different functionalities utilizing readily accessible *N*-(2-aminobenzoyl)benzotriazoles. The free amino group in the substrates did not cause any side reactions except for **6m** and the products were obtained in high yields. The method used in the synthesis has the advantage of operational simplicity, mild reaction condition, ready availability of substrates, and simple reaction work up, compared to literature methods for the preparation of anthranilic acid esters and thioesters.

Column chromatography was performed on silica gel 70–230 mesh. All melting points were determined on a Mettler Toledo apparatus and uncorrected. ^1H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz respectively on a Bruker Advance 500 DPX spectrometer in $CDCl_3$ using TMS as an internal reference. IR spectra of products were obtained on a Perkin Elmer 100 FTIR spectrophotometer. Mass spectral data were taken on a Thermo Finnigan PolarisQ GC-MS spectrometer and Waters SYNAPT MS System HRMS spectrometer. *N*-(2-Aminobenzoyl)benzotriazoles were synthesized by reaction of the corresponding acids with BtH in the presence of DCC following the reported one-step procedure.[20] Other reagents obtained commercially were used without further purification.

2-Aminobenzoates 6a–n and 2-Aminothiobenzoates 7a–i; General Procedure

A mixture of *N*-(2-aminobenzoyl)benzotriazole **8** (1.0 mmol), alcohol (1.2 mmol) or thiol (1.2 mmol), and DMAP (0.122 g, 1.0 mmol) in CH_2Cl_2 (5 mL) was stirred for 6–12 h (**6**) or 4–6 h (**7**) at r.t. After the completion of the reaction, the solvent was removed under reduced pressure. The residue was purified by column chromatography to afford the desired product.

Phenyl 2-Aminobenzoate (6a)

Eluent: EtOAc–hexane, 1:3; white solid; yield: 0.171 g (80%); mp 70–71 °C.

IR (KBr): 3468, 3363, 1691 cm^{-1}.

^1H NMR: δ = 8.14 (d, *J* = 8.0 Hz, 1 H), 7.47 (t, *J* = 7.9 Hz, 2 H), 7.38 (t, *J* = 7.7 Hz, 1 H), 7.31 (t, *J* = 7.2 Hz, 1 H), 7.22 (d, *J* = 8.4 Hz, 1 H), 6.77–6.74 (m, 2 H), 5.81 (br s, 2 H).

^{13}C NMR: δ = 166.9, 151.3, 150.8, 134.9, 131.6, 129.5, 125.8, 122.0, 116.8, 116.4, 109.7.

MS (EI): *m*/*z* = 213.0 [M^+].

HRMS-MALDI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{12}NO_2$: 214.0868; found: 214.0863.

4-Methoxyphenyl 2-Amino-3-methylbenzoate (6b)

Eluent: EtOAc–hexane, 1:3; yellow solid; yield: 0.234 g (91%); mp 136–137 °C.

IR (KBr): 3490, 3361, 1709 cm^{-1}.

^1H NMR: δ = 8.04 (d, *J* = 8.5 Hz, 1 H), 7.29 (d, *J* = 6.0 Hz, 1 H), 7.13 (d, *J* = 7.0 Hz, 2 H), 6.98 (d, *J* = 9.0 Hz, 2 H), 6.69 (t, *J* = 7.5 Hz, 1 H), 5.91 (br s, 2 H), 3.83 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR: δ = 168.7, 158.2, 150.7, 145.2, 136.3, 130.3, 123.8, 123.5, 116.5, 115.2, 109.9, 56.0, 17.6.

MS (EI): *m*/*z* = 257.0 [M^+].

HRMS-MALDI: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}NO_3$: 258.1130; found: 258.1122.

2-Ethoxyethyl 2-Amino-4-methylbenzoate (6c)

Eluent: EtOAc–hexane, 1:4; yellow oil; yield: 0.150 g (67%).

IR (KBr): 3479, 3371, 1689 cm^{-1}.

^1H NMR: δ = 7.81 (d, *J* = 8.5 Hz, 1 H), 6.50–6.49 (m, 2 H), 5.67 (br s, 2 H), 4.43 (t, *J* = 4.8 Hz, 2 H), 3.77 (t, *J* = 5.0 Hz, 2 H), 3.60 (q, *J* = 7.0 Hz, 2 H), 2.29 (s, 3 H), 1.25 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR: δ = 168.0, 150.5, 144.9, 131.4, 117.8, 116.8, 108.4, 68.5, 66.7, 63.4, 21.7, 15.2.

MS (EI): *m*/*z* = 223.1 [M^+].

HRMS-MALDI: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}NO_3$: 224.1287; found: 224.1276.

Phenyl 2-Amino-5-methylbenzoate (6d)

Eluent: EtOAc–hexane, 1:5; yellow solid; yield: 0.178 g (78%); mp 60–61 °C.

IR (KBr): 3486, 3378, 1704 cm^{-1}.

^1H NMR: δ = 7.93 (s, 1 H), 7.47 (t, *J* = 7.8 Hz, 2 H), 7.30 (t, *J* = 8.0 Hz, 1 H), 7.23–7.20 (m, 3 H), 6.68 (d, *J* = 8.0 Hz, 1 H), 5.65 (br s, 2 H), 2.32 (s, 3 H).

^{13}C NMR: δ = 167.9, 151.8, 150.1, 136.9, 131.9, 130.3, 126.5, 126.3, 122.8, 117.7, 110.2, 20.4.

MS (EI): *m*/*z* = 227.1 [M^+].

HRMS-MALDI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}NO_2$: 228.1025; found: 228.1028.

Cyclopentyl 2-Amino-6-methylbenzoate (6e)

Eluent: EtOAc–hexane, 1:4; yellow oil; yield: 0.120 g (55%).

IR (KBr): 3481, 3377, 1683 cm^{-1}.

^1H NMR: δ = 7.09 (t, *J* = 7.8 Hz, 1 H), 6.55 (d, *J* = 7.5 Hz, 2 H), 5.47–5.44 (m, 1 H), 5.15 (br s, 2 H), 2.45 (s, 3 H), 1.99–1.96 (m, 2 H), 1.91–1.89 (m, 2 H), 1.82–1.79 (m, 2 H), 1.70–1.68 (m, 2 H).

^{13}C NMR: δ = 169.1, 149.0, 139.9, 131.8, 120.4, 114.6, 65.9, 32.9, 23.8, 23.0, 15.3.

MS (EI): *m*/*z* = 219.1 [M^+].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{13}H_{18}NO_2$: 220.1338; found: 220.1325.

Cyclohexyl 2-Amino-5-methoxybenzoate (6f)
Eluent: EtOAc–hexane, 1:4; yellow oil; yield: 0.235 g (94%).

IR (KBr): 3479, 3375, 1689 cm^{-1}.

^{1}H NMR: δ = 7.43 (d, *J* = 3.0 Hz, 1 H), 6.97 (dd, *J* = 9.0, 3.0 Hz, 1 H), 6.68 (d, *J* = 8.5 Hz, 1 H), 5.50 (br s, 2 H), 5.03–5.01 (m, 1 H), 3.80 (s, 3 H), 1.98–1.95 (m, 2 H), 1.82–1.80 (m, 2 H), 1.63–1.58 (m, 2 H), 1.50–1.44 (m, 2 H).

^{13}C NMR: δ = 167.3, 150.7, 144.7, 122.4, 118.3, 114.0, 112.0, 72.6, 55.9, 31.7, 25.5, 23.7.

MS (EI): *m/z* = 249.0 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{14}H_{20}NO_3$: 250.1443; found: 250.1444.

Isopropyl 2-Amino-4-chlorobenzoate (6g)
Eluent: EtOAc–hexane, 1:10; yellow oil; yield: 0.178 g (84%).

IR (KBr): 3480, 3372, 1689 cm^{-1}.

^{1}H NMR: δ = 7.81 (d, *J* = 9.0 Hz, 1 H), 6.68 (d, *J* = 2.0 Hz, 1 H), 6.62 (dd, *J* = 8.5, 2.0 Hz, 1 H), 5.84 (br s, 2 H), 5.22 (h, *J* = 6.3 Hz, 1 H), 1.33 (d, *J* = 6.0 Hz, 6 H).

^{13}C NMR: δ = 167.1, 151.2, 139.8, 132.6, 116.6, 115.9, 110.0, 67.9, 22.0.

MS (EI): *m/z* = 213.1 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{10}H_{13}ClNO_2$: 214.0635; found: 214.0634.

Propyl 2-Amino-5-chlorobenzoate (6h)
Eluent: EtOAc–hexane, 1:3; yellow oil; yield: 0.206 g (97%).

IR (KBr): 3485, 3373, 1694 cm^{-1}.

^{1}H NMR: δ = 7.85 (d, *J* = 2.5 Hz, 1 H), 7.23 (dd, *J* = 9.0, 2.5 Hz, 1 H), 6.63 (d, *J* = 9.0 Hz, 1 H), 5.77 (br s, 2 H), 4.25 (t, *J* = 6.8 Hz, 2 H), 1.83–1.79 (m, 2 H), 1.05 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR: δ = 167.3, 149.0, 134.0, 130.4, 120.6, 118.0, 111.8, 66.3, 22.1, 10.6.

MS (EI): *m/z* = 213.2 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{10}H_{13}ClNO_2$: 214.0635; found: 214.0645.

3-Phenylpropyl 2-Amino-5-bromobenzoate (6i)
Eluent: EtOAc–hexane, 1:4; yellow oil; yield: 0.328 g (98%).

IR (KBr): 3487, 3376, 1694 cm^{-1}.

^{1}H NMR: δ = 7.96 (d, *J* = 2.5 Hz, 1 H), 7.34 (t, *J* = 7.5 Hz, 3 H), 7.25 (d, *J* = 7.5 Hz, 3 H), 6.59 (d, *J* = 8.5 Hz, 1 H), 5.79 (br s, 2 H), 4.32 (t, *J* = 6.5 Hz, 2 H), 2.81 (t, *J* = 7.5 Hz, 2 H), 2.16–2.12 (m, 2 H).

^{13}C NMR: δ = 167.1, 149.4, 141.1, 136.8, 133.3, 128.5, 128.4, 126.1, 118.4, 112.2, 107.3, 64.1, 32.4, 30.2.

MS (EI): *m/z* = 333.0 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{16}H_{17}BrNO_2$: 334.0443; found: 334.0438.

4-Chlorophenyl 2-Amino-5-iodobenzoate (6j)
Eluent: EtOAc–hexane, 1:4; pink solid; yield: 0.360 g (97%); mp 96–97 °C.

IR (KBr): 3460, 3353, 1694 cm^{-1}.

^{1}H NMR: δ = 8.36 (d, *J* = 2.0 Hz, 1 H), 7.57 (dd, *J* = 8.8, 2.3 Hz, 1 H), 7.42 (d, *J* = 8.5 Hz, 2 H), 7.15 (d, *J* = 9.0 Hz, 2 H), 6.53 (d, *J* = 9.0 Hz, 1 H), 5.85 (br s, 2 H).

^{13}C NMR: δ = 166.3, 151.6, 149.9, 144.0, 140.5, 132.2, 130.4, 124.0, 119.7, 112.0, 76.4.

MS (EI): *m/z* = 372.9 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{13}H_{10}ClINO_2$: 373.9445; found: 373.9460.

Propyl 2-Amino-3,5-dichlorobenzoate (6k)
Eluent: hexane; white solid; yield: 0.228 g (92%); mp 33–35 °C.

IR (KBr): 3496, 3356, 1698 cm^{-1}.

^{1}H NMR: δ = 7.81 (d, *J* = 2.5 Hz, 1 H), 7.42 (d, *J* = 2.5 Hz, 1 H), 4.26 (t, *J* = 6.8 Hz, 2 H), 1.81 (p, *J* = 7.0 Hz, 2 H), 1.04 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR: δ = 167.8, 146.3, 134.1, 130.1, 121.5, 120.4, 113.2, 67.1, 22.2, 10.6.

MS (EI): *m/z* = 247.0 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{10}H_{12}Cl_2NO_2$: 248.0245; found: 248.0236.

Pentyl 2-Amino-3,5-dibromobenzoate (6l)
Eluent: EtOAc–hexane, 1:4; colorless oil; yield: 0.322 g (88%).

IR (KBr): 3484, 3355, 1694 cm^{-1}.

^{1}H NMR: δ = 7.99 (d, *J* = 2.5 Hz, 1 H), 7.70 (d, *J* = 2.0 Hz, 1 H), 6.39 (br s, 2 H), 4.30 (t, *J* = 6.8 Hz, 2 H), 1.80–1.76 (m, 2 H), 1.43–1.41 (m, 4 H), 0.96 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR: δ = 166.6, 146.6, 139.0, 133.0, 113.0, 111.1, 106.4, 65.4, 28.3, 28.1, 22.4, 14.0.

MS (EI): *m/z* = 362.9 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{12}H_{16}Br_2NO_2$: 363.9548; found: 363.9555.

2-Bromoethyl 2-Amino-4,5-dimethoxybenzoate (6m)
Eluent: CH_2Cl_2); white solid; yield: 0.074 g (24%); mp 95–96 °C.

IR (KBr): 3449, 3341, 1669 cm^{-1}.

^{1}H NMR: δ = 7.35 (s, 1 H), 6.17 (s, 1 H), 5.61 (br s, 2 H), 4.59 (t, *J* = 6 Hz, 2 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.66 (t, *J* = 6.3 Hz, 2 H).

^{13}C NMR: δ = 167.0, 155.2, 147.4, 140.7, 112.6, 101.5, 99.3, 63.4, 56.4, 55.8, 29.2.

MS (EI): *m/z* = 303.0 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{11}H_{15}BrNO_4$: 304.0184; found: 304.0182.

Pent-4-enyl 2-Amino-3,4,5-trimethoxybenzoate (6n)
Eluent: EtOAc–hexane, 1:4; yellow oil; yield: 0.266 g (90%).

IR (KBr): 3492, 3375, 1687 cm^{-1}.

^{1}H NMR: δ = 7.18 (s, 1 H), 5.90–5.85 (m, 1 H), 5.70 (br s, 2 H), 5.09 (dd, *J* = 15.5, 1.5 Hz, 1 H), 5.03 (dd, *J* = 10.0, 1.0 Hz, 2 H), 4.31 (t, *J* = 6.5 Hz, 2 H), 3.97 (s, 3 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 2.23 (q, *J* = 7.2 Hz, 2 H), 1.88 (p, *J* = 7.0 Hz, 2 H).

^{13}C NMR: δ = 167.6, 147.4, 143.5, 140.9, 140.4, 137.6, 115.3, 108.5, 105.1, 63.8, 60.9, 60.3, 56.5, 30.3, 28.0.

MS (EI): *m/z* = 295.1 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{15}H_{22}NO_5$: 296.1498; found: 296.1489.

***S*-2-Mercaptoethyl 2-Aminobenzothioate (7a)**
Eluent: EtOAc–hexane, 1:3; yellow oil; yield: 0.170 g (80%).

IR (KBr): 3479, 3368, 1641 cm^{-1}.

^{1}H NMR: δ = 7.90 (d, *J* = 10.0 Hz, 1 H), 7.30 (t, *J* = 5.0 Hz, 1 H), 6.70–6.67 (m, 2 H), 5.87 (s, 2 H), 3.26 (t, *J* = 5.0 Hz, 2 H), 2.81 (q, *J* = 10.0 Hz, 2 H), 1.72 (t, *J* = 7.5 Hz, 1 H).

^{13}C NMR: δ = 192.1, 148.3, 134.5, 130.2, 118.1, 117.1, 116.4, 32.8, 24.9.

MS (EI): *m/z* = 213.0 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_9H_{12}NOS_2$: 214.0360; found: 214.0358.

_S_-Phenyl 2-Amino-3-methylbenzothioate (7b)
Eluent: EtOAc–hexane, 1:3; yellow solid; yield: 0.268 g (85%); mp 118–120 °C.

IR (KBr): 3497, 3377, 1651 cm^{-1}.

^{1}H NMR: δ = 7.96 (d, *J* = 10.0 Hz, 1 H), 7.56–7.48 (m, 5 H), 7.28 (t, *J* = 7.5 Hz, 1 H), 6.70 (t, *J* = 7.5 Hz, 1 H), 5.95 (br s, 2 H), 2.19 (s, 3 H).

^{13}C NMR: δ = 191.8, 147.8, 135.7, 135.4, 129.4, 129.2, 128.3, 128.2, 123.6, 117.1, 115.9, 17.4.

MS (EI): *m/z* = 243.0 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{14}H_{14}NOS$: 244.0796; found: 244.0791.

Ethyl 2-(2-Amino-3-methylbenzoylthio)acetate (7c)
Eluent: EtOAc–hexane, 1:3; yellow solid; yield: 0.252 g (100%); mp 58–60 °C.

IR (KBr): 3482, 3369, 1741, 1630 cm^{-1}.

^{1}H NMR: δ = 7.83 (d, *J* = 10.0 Hz, 1 H), 5.96 (br s, 2 H), 4.25 (q, *J* = 5.0 Hz, 2 H), 3.83 (s, 2 H), 2.19 (s, 3 H), 1.32 (t, *J* = 5.0 Hz, 3 H).

^{13}C NMR: δ = 191.2, 169.3, 146.8, 135.4, 128.3, 123.5, 117.1, 115.9, 61.8, 31.4, 17.3, 14.2.

MS (EI): *m/z* = 253.0 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_3S$: 254.0851; found: 254.0854.

_S_-Phenyl 2-Amino-4-methylbenzothioate (7d)
Eluent: EtOAc–hexane, 1:3; yellow solid; yield: 0.236 g (97%); mp 101–102 °C.

IR (KBr): 3437, 3346, 1639 cm^{-1}.

^{1}H NMR: δ = 7.92 (d, *J* = 10.0 Hz, 1 H), 7.55–7.47 (m, 5 H), 6.57 (d, *J* = 10.0 Hz, 1 H), 6.50 (s, 1 H), 5.87 (br s, 2 H), 2.32 (s, 3 H).

^{13}C NMR: δ = 190.7, 148.6, 145.8, 135.7, 130.3, 129.1, 128.1, 118.1, 117.2, 115.5, 21.7.

MS (EI): *m/z* = 242.8 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{14}H_{14}NOS$: 244.0796; found: 244.0785.

_S_-2-Mercaptoethyl 2-Amino-5-methylbenzothioate (7e)
Eluent: EtOAc–hexane, 1:3; yellow oil; yield: 0.162 g (71%).

IR (KBr): 3479, 3368, 1641 cm^{-1}.

^{1}H NMR: δ = 7.96 (s, 1 H), 7.13 (d, *J* = 10.0 Hz, 1 H), 6.61 (d, *J* = 10.0 Hz, 1 H), 3.26 (t, *J* = 7.5 Hz, 2 H), 2.81 (q, *J* = 10.0 Hz, 2 H), 2.28 (s, 3 H), 1.72 (t, *J* = 7.5 Hz, 1 H).

^{13}C NMR: δ = 191.9, 146.1, 135.8, 129.7, 125.6, 118.0, 117.3, 32.8, 24.9, 20.4.

MS (EI): *m/z* = 227.0 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{10}H_{14}NOS_2$: 228.1025; found: 228.1030.

Ethyl 2-(2-Amino-4,5-dimethoxybenzoylthio)acetate (7f)
Eluent: CH_2Cl_2; yellow solid; yield: 0.268 g (90%); mp 117–119 °C.

IR (KBr): 3468, 3355, 1733, 1635 cm^{-1}.

^{1}H NMR: δ = 7.28 (d, *J* = 10.0 Hz, 1 H), 6.13 (s, 1 H), 5.88 (br s, 2 H), 4.26 (q, *J* = 10.0 Hz, 2 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.84 (s, 2 H), 1.33 (t, *J* = 7.5 Hz, 2 H).

^{13}C NMR: δ = 189.8, 169.4, 155.7, 145.5, 140.9, 111.4, 109.4, 99.2, 61.8, 56.5, 55.9, 31.3, 14.2.

MS (EI): *m/z* = 299.2 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{13}H_{17}NO_5S$: 299.0827; found: 299.0820.

Ethyl 2-(2-Amino-4-chlorobenzoylthio)acetate (7g)
Eluent: EtOAc–hexane, 1:3; yellow solid; yield: 0.248 g (91%); mp 108–110 °C.

IR (KBr): 3472, 3355, 1734, 1655 cm^{-1}.

^{1}H NMR: δ = 7.82 (d, *J* = 10.0 Hz, 1 H), 6.68–6.65 (m, 2 H), 5.96 (br s, 2 H), 4.25 (q, *J* = 7.5 Hz, 2 H), 3.83 (s, 2 H), 1.33 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR: δ = 190.2, 169.0, 149.1, 140.9, 131.6, 116.9, 116.3, 116.1, 61.9, 31.3, 14.2.

MS (EI): *m/z* = 273.0 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{11}H_{13}ClNO_3S$: 274.0305; found: 274.0316.

_S_-Phenyl 2-Amino-5-bromobenzothioate (7h)
Eluent: EtOAc–hexane, 1:3; yellow solid; yield: 0.282 g (92%); mp 146–148 °C.

IR (KBr): 3485, 3371, 1653 cm^{-1}.

^{1}H NMR: δ = 8.14 (d, *J* = 5.0 Hz, 1 H), 7.54–7.49 (m, 5 H), 7.39 (dd, *J* = 10.0, 5.0 Hz, 1 H), 6.60 (d, *J* = 5.0 Hz, 1 H), 5.86 (br s, 2 H).

^{13}C NMR: δ = 190.7, 147.4, 137.4, 135.6, 132.3, 129.7, 129.3, 127.3, 118.9, 118.8, 107.4.

MS (EI): *m/z* = 307.0 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_{13}H_{11}BrNOS$: 307.9745; found: 307.9751.

_S_-Ethyl 2-Amino-5-iodobenzothioate (7i)
Eluent: EtOAc–hexane, 1:3; yellow solid; yield: 0.295 g (96%); mp 76–78 °C.

IR (KBr): 3421, 3319, 1628 cm^{-1}.

^{1}H NMR: δ = 8.16 (s, 1 H), 7.50 (d, *J* = 10.0 Hz, 1 H), 6.48 (d, *J* = 10.0 Hz, 1 H), 5.85 (br s, 2 H), 3.05 (q, *J* = 10.0 Hz, 2 H), 1.36 (t, *J* = 5.0 Hz, 3 H).

^{13}C NMR: δ = 192.3, 147.3, 142.3, 138.4, 120.8, 119.3, 75.8, 23.5, 14.8.

MS (EI): *m/z* = 307.0 [M$^+$].

HRMS-MALDI: *m/z* [M + H]$^+$ calcd for $C_9H_{11}INOS$: 307.9606; found: 307.9621.

Acknowledgment

It is gratefully acknowledged that this work was supported financially by Anadolu University (Project No: 1002F88) and we are also grateful to AUBIBAM for providing ^{1}H and ^{13}C NMR spectra.

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