STRUCTURAL ANALOGUES OF THIOFLAVIN T - NEW SYNTHETIC APPROACH

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Abstract

Thioflavin T (ThT) is a benzothiazolium salt used to visualize and quantify the presence of amyloid plaques found in the brains of chronic neurodegenerative disease patients. Here we propose an effective one-pot approach for the synthesis of six Thioflavin T analogues via amidoalkylation/oxidation/alkylation sequence. The conditions for multicomponent reactions of benzothiazole or thiazole, alkyl chloroformates and N,N-dimethylaniline were studied and optimized.

Keywords: *Thioflavin T, α-amidoalkylation, multicomponent reactions, oxidation, alkylation*

1. INTRODUCTION

Thioflavin T (*ThT*, *Basic Yellow 1*, Figure 1) is a benzothiazole dye that exhibits enhanced fluorescence upon binding to *β*-amyloid plaques both *in vitro* or *in vivo*. Since its first description in 1959 [1], *ThT* has found many applications and nowadays is commonly used for the diagnosis of Alzheimer's and Parkinson's diseases [2-4]. In addition to that, *ThT* easily binds to DNA and RNA [5, 6] and has been also applied as fluorescent and luminescence biosensor for nucleic acid or insulin studying [7-10]. In this regard new methods for the synthesis of its derivatives and their use in diagnosis and therapy of chronic neurodegenerative diseases are constantly reported [11, 12].

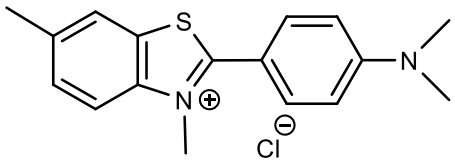


Figure 1 *Thioflavin T*

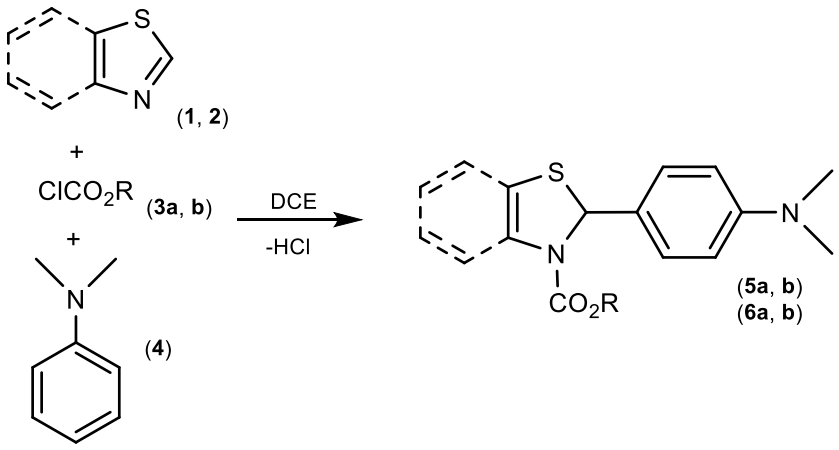
It is known that thiazole-containing compounds show wide range of biological activities [13, 14]. In recent years their successful application as dyes in optoelectronics [15], CN-sensors [16] and fluorescent materials [17, 18] has also been reported. Research groups demonstrated the synthesis of various benzothiazole-based compounds as *β*-amyloid plaques imaging agents [19-22].

The mainly employed method described in literature for the synthesis of 2-aryl benzothiazoles containing an aniline fragment is based on the cyclocondensation of 2-aminothiophenol and aromatic aldehydes [23-27] or carboxylic acids [28]. Other synthetic strategies include cyclization reactions of bis-(2-benzalaminophenyl)disulfides [29, 30] or thiophenolic Schiff bases [31]. Methods of direct arylation of thiazole [32] and cross-coupling of heteroaryl thiols with arylzinc reagents [33] have also been investigated. All of these reactions are carried out in the presence of various catalysts that are not always easily accessible. From a synthetic point of view, it is interesting to develop new methods for synthesis of structural derivatives with potential biological activity.

In previously published articles we proposed a new two-stage method for the synthesis of phytoalexin *Camalexin* and its analogues by coupling of various aza-aromatics and indole or pyrrole in an amidoalkylation–oxidation sequence [34, 35]. Taking this into account, herein we expand the scope of our previously published work with the synthesis of six new *Thioflavin T* analogues.

2. RESULTS AND DISCUSSION

We have developed an efficient multicomponent one-pot method for the synthesis of *p*-(2-thiazolyl)-*N*,*N*-dimethylanilines (**5a**, **b**) and (**6a**, **b**) through the reaction of benzothiazole (**1**) or thiazole (**2**), alkyl chloroformates (**3a**, **b**) and *N*,*N*-dimethylaniline (**4**) (Scheme 1). The reaction conditions were optimized by varying the solvent, temperature and time.



Scheme 1 One-pot approach for the synthesis of *p*-substituted *N*,*N*-dimethylanilines (**5**, **6**)

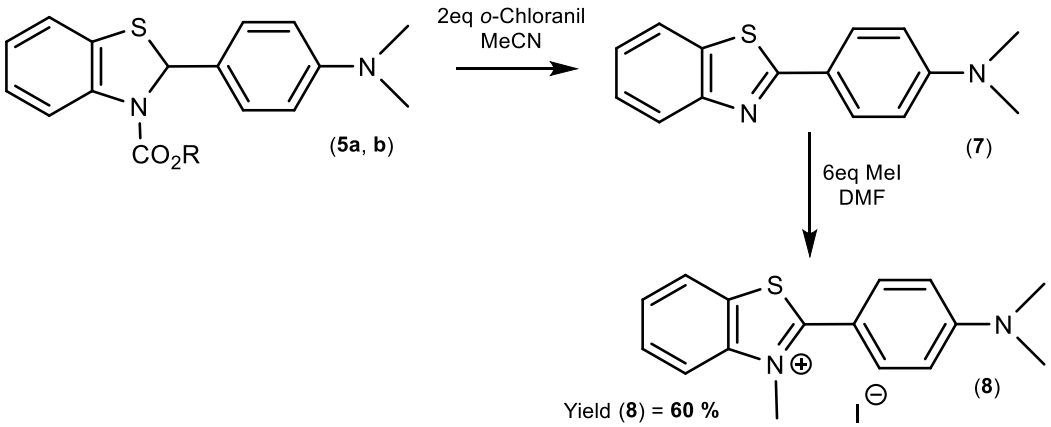
Table 1 Reaction conditions and yields of amidoalkylated *N*,*N*-dimethylanilines (**5a**, **b**) and (**6a**, **b**)

N-heterocycle	Product	R	Conditions	Yield, %	mp, °C
Benzothiazole (**1**)	(**5a**)	Et	80 h, 25 °C 3 h, 60 °C	67 91	Oil
	(**5b**)	Me	80 h, 25 °C 3 h, 60 °C	40 86	89 – 92
Thiazole (**2**)	(**6a**)	Et	60 h, 0 – 25 °C 100 h, 0 – 4 °C	54 64	Oil
	(**6b**)	Me	60 h, 0 – 25 °C 100 h, 0 – 4 °C	64 71	104 – 107

Dichloroethane was found to be the optimal solvent for all of the studied reactions. Although all reactions proceeded at room temperature (25 °C), in some cases the yields were not satisfactory. In search of higher yields of amidoalkylated products we found that the optimal conditions (for benzothiazole as a starting material) were 3 h at 60 °C while for thiazoles lower temperature (0 – 4 °C) and longer time (4 days) gave better results. In the case of thiazole the amidoalkylation took place with one equivalent of *N*,*N*-dimethylaniline, in the absence of additional base. For the reactions with benzothiazole the presence another equivalent of *N*,*N*-dimethylaniline was important.

When the reactions with benzothiazole were carried out in dichloroethane at 60 °C for 3 hours, the yields of the isolated products were higher (91 % for **5a** and 86 % for **5b**, after column chromatography purification) (Table 1). The yields obtained with thiazole as the starting material under optimized conditions (4 days, 0 – 4 °C) are satisfactory (64 % for **6a** and 71 % for **6b**).

The results of the performed *α*-amidoalkylation reactions are summarised in Table 1.



Scheme 2 Synthesis of 2-(*p*-(dimethylamino)phenyl)-3-methylbenzothiazolium iodide (**8**)

Table 2 Reaction conditions and yields of product (**7**)

Starting material	*o*-Chloranil oxidation			mp (**7**), °C
	T, °C	Time, h	Yield (**7**), %	
(**5a**)	60	2	51	171 – 173
(**5b**)	60	2	57	

Next, we proceeded with experiments to remove the alkoxycabonyl groups and rearomatize the benzothiazole moiety in the obtained products (**5a**, **b**). This was successfully accomplished by oxidation of (**5a**, **b**) with *o*-Chloranil (Scheme 2, Table 2). The oxidation reactions were accompanied with formation of unidentified byproduct (observed by TLC), which lead to significant losses of starting material and decreased the yield of the target product (**7**).

The obtained product (**7**) was successfully alkylated following the Garmaise procedure to 2-(4-(dimethylamino)phenyl)-3-methylbenzo[d]thiazol-3-ium iodide (**8**, Scheme 2) [36].

Spectroscopic methods were used to determine the structure of compounds (**5**, **6**). Figures 2 and 3 show the ^{1}H-NMR spectra of the compounds (**5a**) and (**6b**). In the ^{1}H-spectra of compounds (**5a**, **b**) and (**6a**, **b**) measured in DMSO-d_6 at 80 °C (600 MHz) we observed two apparent doublets in the range δ = 6.63 – 6.67 ppm and 7.10 – 7.17 ppm, corresponding to the aromatic protons of *N*,*N*-dimethylaniline. The presence of these doublets is sufficient evidence for the substitution pattern of the benzene ring and the position of the newly formed C-C bond.

Figure 4 shows ^{1}H-NMR spectra of product (**7**) with successfully rearomatized benzothiazole moiety.

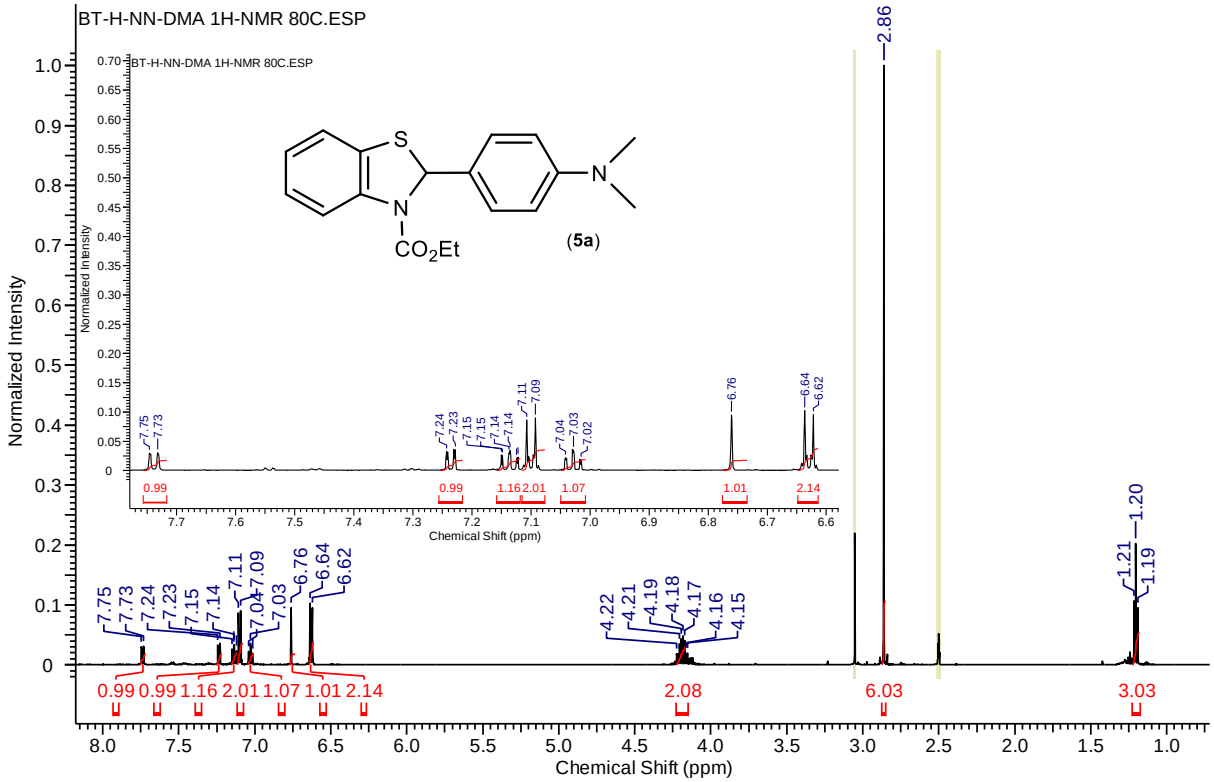


Figure 2 ^{1}H-NMR spectra of (**5a**) - DMSO-d_6 - 80 °C (600 MHz)

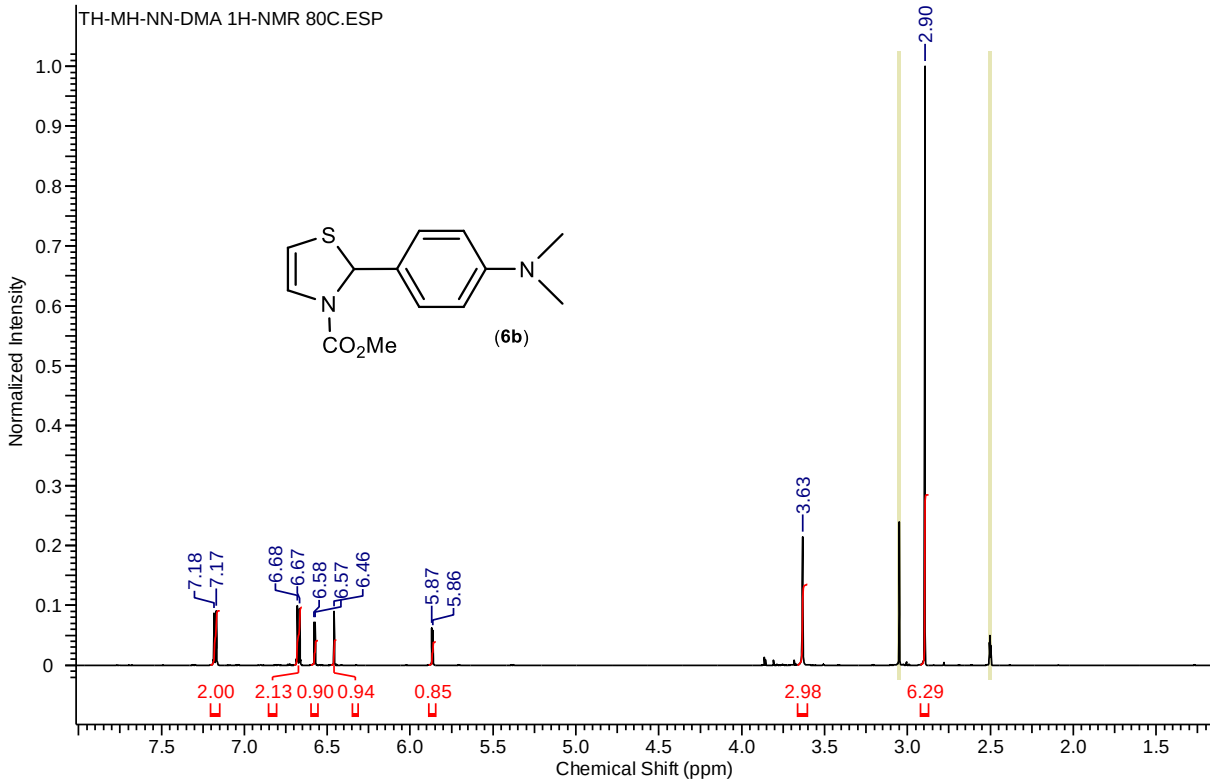


Figure 3 ^{1}H-NMR spectra of (**6b**) - DMSO-d_6 - 80 °C (600 MHz)

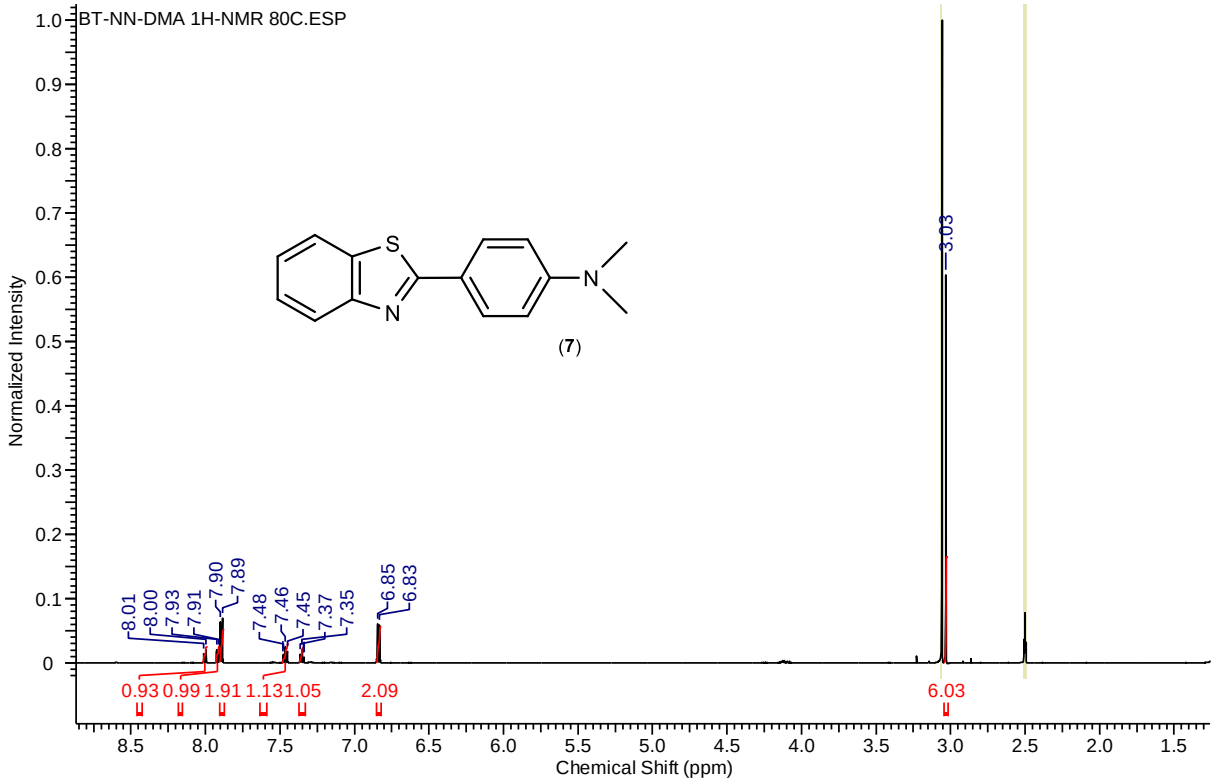


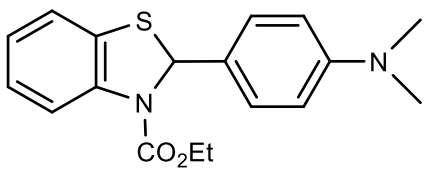
Figure 4 ^{1}H-NMR spectra of (**7**) - DMSO-d_6 - 80 °C (600 MHz)

3. EXPERIMENTAL

General information: Commercial solvents and reagents, such as benzothiazole, thiazole, acyl chlorides and *N*,*N*-dimethylaniline were purchased from Sigma-Aldrich or Merck and were used without further purification. Melting points were determined on a Boetius PHMKO5 hot stage apparatus and are uncorrected. IR spectra were measured on VERTEX 70 FT-IR spectrometer (Bruker Optics, Germany). ^{1}H-, ^{13}C-NMR spectra were measured on Bruker Avance AV600 spectrometers and chemical shifts (δ, ppm) are downfield from TMS. NMR spectra were taken at 80 °C in DMSO-d_6. TLC was done on precoated 0.2 mm Merck silica gel 60 plates. Silica gel and neutral alumina were used for column chromatographic separation.

One-pot approach for the synthesis of products (**5a**, **b**) ***and*** (**6a**, **b**):

To benzothiazole, thiazole (1 mmol) dissolved in dry dichloroethane (10 mL) were added ethyl chloroformate (1.2 mmol) or methyl chloroformate (2 mmol) and *N*,*N*-dimethylaniline (2 mmol for benzothiazole or 1 mmol for thiazole). The reaction mixture is magnetically stirred for the time and temperature specified in Table 1. After completion of the reaction (monitored by TLC), the mixture is transferred to a separatory funnel with dichloromethane (20 – 30 mL/mmol) and is consecutively extracted with equal volumes of aqueous Na_2CO_3 (3 %), water and brine. The combined organic layers are dried (Na_2SO_4) and the solvent is removed under reduced pressure. Analytically pure samples were obtained by column chromatography on silica gel, using petroleum ether (increasing polarity to petroleum/diethyl ether 8:1) as eluents.



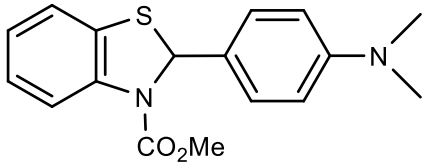
Ethyl 2-(4-(dimethylamino)phenyl)benzo[d]thiazole-3(2H)-carboxylate (**5a**)**:**

Yield: 67, 91 %; Colorless oil;

^{1}H-NMR (600 MHz, 80 °C, DMSO-d_6, δ ppm, *J* Hz): 1.20 (t, *J* = 7, 3H, -$CO_2CH_2\underline{CH_3}$), 2.86 (s, 6H, -$N(\underline{CH_3})_2$), 4.15 – 4.22 (m, 2H, -$CO_2\underline{CH_2}CH_3$), 6.63 (d, *J* = 8.8, 2H, Ar(*N*,*N*-dimethylaniline)), 6.76 (s, 1H, -CH), 7.03 (t, *J* = 7.6, 1H, Ar(benzothiazole)), 7.10 (d, *J* = 8.8, 2H, Ar(*N*,*N*-dimethylaniline)), 7.14 (t, *J* = 7.6, 1H, Ar(benzothiazole)), 7.23 (d, *J* = 8.2, 1H, Ar(benzothiazole)), 7.74 (d, *J* = 8.2, 1H, Ar(benzothiazole));

^{13}C-NMR (150 MHz, 80 °C, DMSO-d_6, δ ppm): 14.6, 40.4, 62.4, 66.7, 112.6, 117.2, 122.8, 124.6, 125.6, 126.4, 128.8, 130.1, 138.3, 151.0, 152.7;

IR (KBr, cm^{-1}): 3054, 2961, 1719, 1620, 1518, 1470, 1430, 1351, 1282, 1237, 1189, 749;



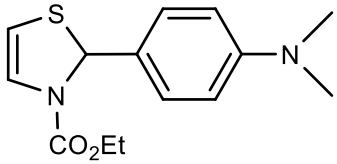
Methyl 2-(4-(dimethylamino)phenyl)benzo[d]thiazole-3(2H)-carboxylate (**5b**)**:**

Yield: 40, 86 %; White solid; mp: 89 – 92 °C;

^{1}H-NMR (600 MHz, 80 °C, DMSO-d_6, δ ppm, *J* Hz): 2.87 (s, 6H, -$N(\underline{CH_3})_2$), 3.75 (s, 3H, -$CO_2\underline{CH_3}$), 6.64 (d, *J* = 9.1, 2H, Ar(*N*,*N*-dimethylaniline)), 6.78 (s, 1H, -CH), 7.01 – 7.08 (m, 1H, Ar(benzothiazole)), 7.11 (d, *J* = 9.1, 2H, Ar(*N*,*N*-dimethylaniline)), 7.14 – 7.19 (m, 1H, Ar(benzothiazole)), 7.25 (d, *J* = 7.6, 1H, Ar(benzothiazole)), 7.75 (d, *J* = 7.6, 1H, Ar(benzothiazole));

^{13}C-NMR (150 MHz, 80 °C, DMSO-d_6, δ ppm): 40.0, 53.0, 66.2, 112.2, 116.8, 122.3, 124.3, 125.1, 125.8, 129.5, 131.9, 137.7, 150.5, 152.7;

IR (KBr, cm^{-1}): 3064, 2954, 1723, 1615, 1523, 1468, 1437, 1344, 1273, 1240, 1191, 747;



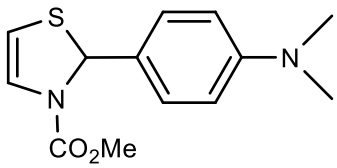
Ethyl 2-(4-(dimethylamino)phenyl)thiazole-3(2H)-carboxylate (**6a**)**:**

Yield: 54, 64 %; Pale yellow oil;

^{1}H-NMR (600 MHz, 80 °C, DMSO-d_6, δ ppm, *J* Hz): 1.30 (t, *J* = 7, 3H, -$CO_2CH_2\underline{CH_3}$), 2.89 (s, 6H, -$N(\underline{CH_3})_2$), 4.30 – 4.34 (m, 2H, -$CO_2\underline{CH_2}CH_3$), 5.85 (d, *J* = 4.7, 1H, Ar(thiazole)), 6.45 (s, 1H, -CH), 6.57 (d, *J* = 4.7, 1H, Ar(thiazole)), 6.66 (d, *J* = 8.8, 2H, Ar(*N*,*N*-dimethylaniline)), 7.18 (d, *J* = 8.8, 2H, Ar(*N*,*N*-dimethylaniline));

^{13}C-NMR (150 MHz, 80 °C, DMSO-d_6, δ ppm): 14.3, 40.5, 62.1, 65.1, 103.7, 112.6, 119.9, 122.8, 126.7, 130.5, 151.0;

IR (KBr, cm^{-1}): 3094, 2962, 1704, 1615, 1524, 1447, 1352, 1260, 1240, 1192, 751;



Methyl 2-(4-(dimethylamino)phenyl)thiazole-3(2H)-carboxylate (6b):

Yield: 64, 71 %; White solid; mp: 104 – 107 °C;

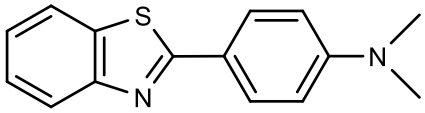
^{1}H-NMR (600 MHz, 80 °C, DMSO-d_6, δ ppm, *J* Hz): 2.90 (s, 6H, -N($\underline{CH_3}$)$_2$), 3.63 (s, 3H, -$CO_2\underline{CH_3}$), 5.86 (d, *J* = 4.7, 1H, Ar(thiazole)), 6.46 (s, 1H, -CH), 6.57 (d, *J* = 4.7, 1H, Ar(thiazole)) 6.67 (d, *J* = 8.8, 2H, Ar(*N*,*N*-dimethylaniline)), 7.17 (d, *J* = 8.8, 2H, Ar(*N*,*N*-dimethylaniline));

^{13}C-NMR (150 MHz, 80 °C, DMSO-d_6, δ ppm): 40.4, 53.3, 65.6, 104.0, 112.6, 121.4, 121.5, 126.6, 130.4, 153.2;

IR (KBr, cm^{-1}): 3111, 2958, 1708, 1619, 1532, 1449, 1347, 1252, 1247, 1184, 758;

***Oxidation of amidoalkylated N,N-dimethylanilines* (5a, b) *to* 4-(benzo[d]thiazol-2-yl)-*N*,*N*-dimethylaniline (7):**

The corresponding compound (**5**) (0.5 mmol) is dissolved in acetonitrile (8 mL), then the oxidant *o*-Chloranil (2 equiv.) is added and the reaction mixture is stirred (Table 2). After completion of the reaction (monitored by TLC) the solvent is evaporated under reduced pressure and the mixture is then dry-loaded onto neutral alumina. Chromatography on a short alumina column with petroleum/diethyl ether (8:1) as the eluent gave 4-(benzo[d]thiazol-2-yl)-*N*,*N*-dimethylaniline (**7**) in yields indicated in Table 2.



4-(benzo[d]thiazol-2-yl)-*N*,*N*-dimethylaniline (7):

Yield: 51, 57 %; Yellow solid; mp: 171 – 173 °C; (mp^{lit}: 173 °C) [25]; (mp^{lit}: 170 – 172 °C) [29];

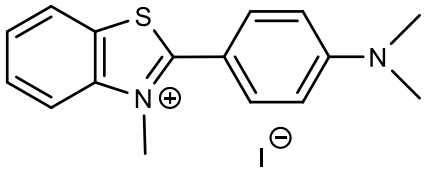
^{1}H-NMR (600 MHz, 80 °C, DMSO-d_6, δ ppm, *J* Hz): 3.03 (s, 6H, -N($\underline{CH_3}$)$_2$), 6.84 (d, *J* = 8.8, 2H, Ar(*N*,*N*-dimethylaniline)), 7.35 (t, *J* = 7.6, 1H, Ar(benzothiazole)), 7.46 (t, *J* = 7.6, 1H, Ar(benzothiazole)), 7.89 (d, *J* = 8.8, 2H, Ar(*N*,*N*-dimethylaniline)), 7.92 (d, *J* = 8.2, 1H, Ar(benzothiazole)), 8.00 (d, *J* = 8.2, 1H, Ar(benzothiazole));

^{13}C-NMR (150 MHz, 80 °C, DMSO-d_6, δ ppm): 40.4, 112.4, 119.9, 121.0, 122.2, 122.4, 123.0, 124.8, 126.6, 129.0, 134.5, 168.3;

IR (KBr, cm^{-1}): 3056, 2908, 1609, 1485, 1368, 1228, 1189, 752;

***Alkylation of* 4-(benzo[d]thiazol-2-yl)-*N*,*N*-dimethylaniline (7) *to* 2-(4-(dimethylamino)phenyl)-3-methylbenzo[d]thiazol-3-ium iodide (8):**

4-(benzo[d]thiazol-2-yl)-*N*,*N*-dimethylaniline (**7**) (0.3 mmol) is dissolved in dimethylformamide (8 mL), then methyl iodide (6 equiv.) is added and the reaction mixture is refluxed for 10 hours. The benzothiazolium salt is crystallized after cooling from diethyl ether. The yellow solid compound was filtered, washed with diethyl ether and dried.



2-(4-(dimethylamino)phenyl)-3-methylbenzo[d]thiazol-3-ium iodide (8):

Yield: 60 %; Yellow solid; mp: 223 – 226 °C; (mp^{lit}: 223 – 224 °C) [36];

IR (KBr, cm^{-1}): 3012, 2952, 1483, 1403, 1322, 770;

4. CONCLUSIONS

New efficient synthetic approach for the synthesis of six structural analogues of Thioflavin T is demonstrated. The presented methodology offers several advantages, such as simple catalyst-free procedure, clean reaction conditions and good yields.

ACKNOWLEDGMENTS

We gratefully acknowledge funding from the Scientific Research Fund of the Bulgarian Ministry of Education and Science (Grant DN09/15-2016) and the University of Plovdiv (Grant MU19-HF012).

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