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PTSA catalyzed straightforward protocol for the synthesis of 2-(*N*-acyl)aminobenzimidazoles and 2-(*N*-acyl) aminobenzothiazoles in PEG

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ABSTRACT

An efficient PTSA catalyzed synthesis of 2-(*N*-acyl)aminobenzimidazoles and 2-(*N*-acyl)aminobenzothiazoles has been described using *S*-ethylated-*N*-acylthioureas as substrates and polyethylene glycol as solvent.

2-Aminobenzimidazoles and 2-aminobenzothiazoles have elicited considerable interest among medicinal chemists because these are privileged in many pharmaceutical agents as well as in natural products.[1] In particular, compounds containing 2-(*N*-acyl)aminobenzimidazole (2-NABI) and 2-(*N*-acyl)aminobenzothiazole (2-NABT) sub structures exhibit a wide range of biological activities such as antimicrobial,[2] antiinflammatory,[3] anticancer,[4] and antiviral[5] activities. 2-NABI are found to be potent inhibitors in several receptor ligands like interleukin-2-inducible T-cell kinase (**ITK**), vascular endothelial growth factor receptor-2 (**VEGFR-2**) and rapidly accelerated fibrosarcoma kinase (**RAFK**)[6–8] etc. Moreover, these scaffolds can also act as intermediates in the synthesis of many commercially available drugs like Mebendazole.[9,10] Owing to their significant utility in both pharmaceutical and medicinal chemistry, various synthetic methodologies for the synthesis of 2-NABI[10–12] and 2-NABT[13] have been reported. Generally, these methods involved acylation of 2-aminobenzimidazoles and 2-aminobenzothiazoles, respectively. Moreover, 2-NABI have also been synthesized via cyclo-desulfurization of pre-formed thioureas using various desulfonating agents such as HgO,[14] PS-carbodiimide,[15] BOP/DBU,[16] and EDC.[17] However, these methods have some drawbacks such as formation of a mixture of regio isomers in conventional acylation, use of either expensive or toxic reagents and solvents, and requirement of long reaction times in oxidative cyclizations. Therefore, development of an efficient method to synthesize 2-NABI and 2-NABT is still highly desirable.

Hazardous, toxic, and volatile organic solvents are being continuously replaced either by the use of solvent-free techniques[18] or by using water,[19] phase-transfer catalysts,[20] ionic liquids,[21] polyethylene glycol (PEG),[22] etc. PEG is found to be an interesting eco-friendly solvent system in synthetic organic chemistry with unique properties such as nontoxicity, inexpensive nature, and being a nonionic liquid solvent of low volatility. To the best of our knowledge, no reports have been reported for the direct synthesis of 2-NABI and 2-NABT from *S*-ethylated-*N*-acylthioureas using BrØnsted acids. Thus, in continuation of our work on the development of environmentally benign new synthetic methodologies for the synthesis of heterocyclic compounds,[23] herein, we report that PEG-400 mediated PTSA catalyzed a simple and straightforward protocol for the synthesis of 2-NABI and 2-NABT from *S*-ethylated-*N*-acylthioureas[24] and *O*-phenylenediamines and *O*-aminothiophenols (Scheme 1).

In order to investigate the reaction conditions for the synthesis of 2-NABI (**3**), we have chosen the reaction of *S*-ethyl-*N*-benzoylthiourea (**1a**) with readily available diamine (**2a**) as a model

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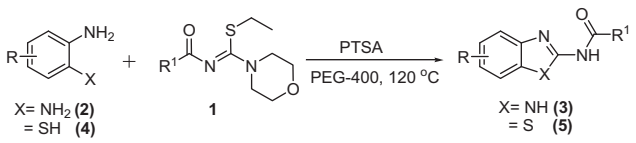
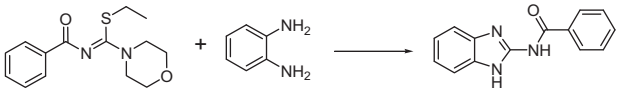


Scheme 1. Synthesis of 2-(*N*-acyl)aminobenzimidazoles (**3**) and 2-(*N*-acyl)aminobenzothiazoles (**5**).

reaction. Thus, *O*-phenylenediamine (1.7 mmol) (**2a**) was treated with *S*-ethyl-*N*-benzoylthiourea (1.8 mmol) (**1a**) at 120 °C under solvent free conditions. In the absence of catalyst the product was obtained in very low yield after a prolonged time. Therefore, our efforts were focused on the search for a suitable catalyst. Initially, Lewis acid $ZnCl_2$ (30 mol %) was chosen as a catalyst to carry out this reaction. As a result, very low yields were observed after a prolonged time. Attempts with BrØnsted acid, trifluoroacetic acid (TFA) as a catalyst were successful. The reaction was found to furnish 25% of yield within 6 hours. Encouraged by this result, we turned our attention to various BrØnsted acids. They were screened in our model reaction (Table 1, entries 3–6). Finally, we found that PTSA showed high catalytic activity in terms of reaction time as well as yield of the product. The effect of amount of catalyst on the conversion and rate of the reaction was studied by varying the amount of PTSA under solvent free conditions (Table 1, entries 6–9). It was found that 30 mol % of PTSA was sufficient to carry out the reaction smoothly (Table 1, entry 6). An increase in the amount of PTSA more than 30 mol % showed no significant improvement in the yield, whereas the yield was reduced by decreasing the amount of PTSA to 10 mol %. We then evaluated the effect of various solvents on the model reaction. As it can be seen in Table 1, the best results were obtained by heating the reaction mixture in PEG-400 at 120 °C and other protic solvents also gave better yields at their reflux temperatures. But, aprotic solvents were not suitable for the purpose.

Table 1
Optimization of reaction conditions to **3a**[a]



Entry	Catalyst (mol %)	Solvent (5 vol.)	Time (h)	Yield[b] (%)
1	—	—	20	Trace
2	$ZnCl_2$ (30)	—	13	10
3	TFA (30)	—	6	25
4	AA (30)	—	6	32
5	BSA (30)	—	6	45
6	PTSA (30)	—	4	52
7	PTSA (40)	—	4	52
8	PTSA (20)	—	4	45
9	PTSA (10)	—	4	35
10	PTSA (30)	Toluene	24	32[c]
11	PTSA (30)	THF	24	40[c]
12	PTSA (30)	1,4-Dioxane	24	45[c]
13	PTSA (30)	MeOH	20	60[c]
14	PTSA (30)	EtOH	15	65[c]
15	PTSA (30)	IPA	4	70[c]
16	PTSA (30)	*n*-BuOH	4	70[c]
17	PTSA (30)	PEG-400	4	76

TFA, trifluoroacetic acid; AA, acetic acid; BSA, benzene sulfonic acid; PTSA, *p*-toluene sulfonic acid.

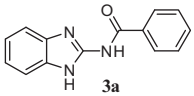
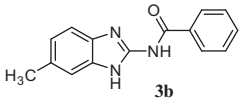
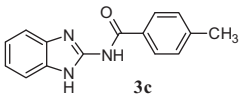
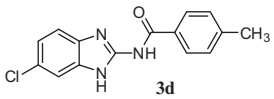
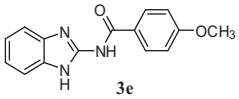
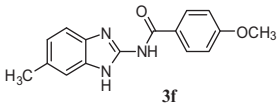
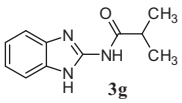
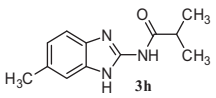
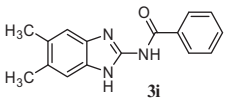
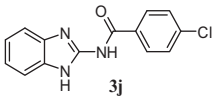
[a] *S*-Ethyl-*N*-benzoylthiourea (**1a**) (1.8 mmol), *O*-phenylenediamine (1.7 mmol) (**2a**) at 120 °C.

[b] Isolated yields.

[c] At reflux temperature.

With the optimized conditions in hand,[25] the scope of the reaction substrates was investigated. First, we examined the reaction with different *O*-phenylenediamines and the results are listed in Table 2. It was found that various substrates were converted into the corresponding products with good yields under the optimized conditions. *O*-Phenylenediamines having electron-withdrawing groups gave slightly lower yields (Table 2, entry 4) when compared to *O*-phenylenediamines having electron-donating groups. Next, different *S*-ethylated-*N*-acylthioureas were investigated as the reaction substrates (Table 2). The presence of electron-withdrawing or electron-donating substituents on the aromatic ring of *S*-ethyl-*N*-benzoylthioureas makes some differences in the yields of the reaction. It seems that electron-withdrawing groups on the aromatic ring are unfavorable for the reaction, only a moderate yield was obtained with *S*-ethyl-*N*-(4-chlorobenzoyl)thiourea as the substrate (Table 2, entry 10). Aliphatic substituted *S*-ethylated thiourea was a good substrate as well (Table 2, entries 7 and 8).

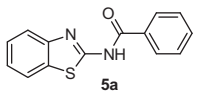
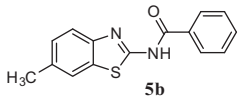
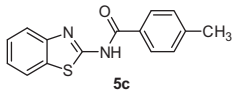
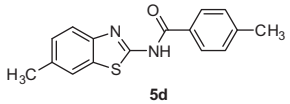
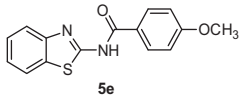
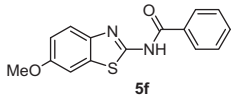
Table 2
Synthesis of 2-NABI (**3**)[a]

Entry	R	R^1	Product (3)	Yield[b] (%)
1	H	Ph	 **3a**	76
2	4-Me	Ph	 **3b**	73
3	H	4-MePh	 **3c**	78
4	4-Cl	4-MePh	 **3d**	60
5	H	4-OMePh	 **3e**	77
6	4-Me	4-OMePh	 **3f**	70
7	H	*i*-Pr	 **3g**	70
8	4-Me	*i*-Pr	 **3h**	68
9	4,5-Me	Ph	 **3i**	70
10	H	4-ClPh	 **3j**	45

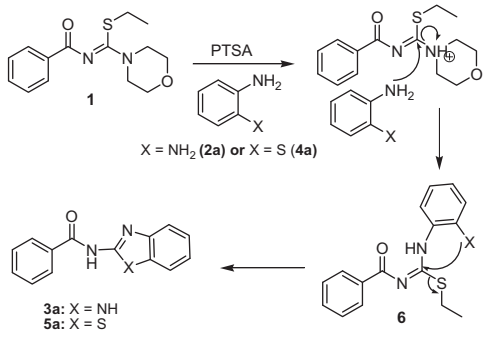
[a] *S*-Ethyl-*N*-acylthiourea (**1**) (1.8 mmol), *O*-phenylenediamine (**2**) (1.7 mmol), PEG-400 (5 vol.) and PTSA (30 mol %) at 120 °C.

[b] Isolated yields.

Table 3
Synthesis of 2-NABT (**5**)[a]

Entry	R	R^1	Product (5)	Yield[b] (%)
1	H	Ph	 **5a**	72
2	5-Me	Ph	 **5b**	68
3	H	4-MePh	 **5c**	70
4	5-Me	4-MePh	 **5d**	72
5	H	4-OMePh	 **5e**	75
6	5-OMe	Ph	 **5f**	73

[a] *S*-Ethyl-*N*-acylthiourea (**1**) (1.8 mmol), *O*-aminothiophenol (**4**) (1.7 mmol), PEG-400 (5 vol.), and PTSA (30 mol %) at 120 °C.
[b] Isolated yields.



Scheme 2.

After successfully synthesizing a series of 2-(*N*-acyl)aminobenzimidazoles in good yields under the above optimized conditions, we turned our attention toward the synthesis of 2-(*N*-acyl)aminobenzothiazole derivatives (**5**). We carried out the reaction with *O*-aminothiophenol (1.7 mmol) and *S*-ethyl-*N*-benzoylthiourea (1.8 mmol) in the presence of 30 mol % PTSA in PEG-400 (0.5 mL) at 120 °C. The reaction was completed within 5 h and the product was obtained in good yield. Using the optimized reaction conditions, we synthesized a variety of 2-(*N*-acyl)aminobenzothiazoles with different *S*-ethyl-*N*-acylthioureas and *O*-aminothiophenols and the results are summarized in Table 3. All the synthesized compounds were fully characterized by advanced spectroscopic analysis (^{1}H NMR, ^{13}C NMR, and Mass).

In summary, we have developed a PEG mediated PTSA catalyzed novel and straightforward protocol for the synthesis of a wide variety of 2-(*N*-acyl)aminobenzimidazoles and 2-(*N*-acyl)aminobenzothiazoles from *S*-ethylated-*N*-acylthioureas. In contrast to the traditional synthetic methods for 2-NABI and 2-NABT, the reaction procedure was eco-friendly, and the reagents were inexpensive. Therefore, this method is an attractive alternative to synthesize 2-NABI and 2-NABT.

To explain the formation of 2-NABI (**3**) and 2-NABT (**5**), a plausible mechanism is shown in Scheme 2. This mechanism involves the initial protonation of nitrogen on morpholine by PTSA, followed by the addition of *O*-phenylenediamine (**2a**) or *O*-aminothiphenol (**4a**) to form **6** through the elimination of morpholine. Finally, intramolecular cyclization of **6** occurs through the elimination of ethyl mercaptane to form 2-NABI (**3**) or 2-NABT (**5**).

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Supplementary data

Supplementary data (general experimental procedure, characterization data and ^{1}H, ^{13}C NMR and mass spectra of all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.040.

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25. *General experimental procedure for the synthesis of (**3**) and (**5**):* A mixture of *S*-ethyl-*N*-acylthiourea (**1**) (1.8 mmol), *O*-phenylenediamine (**2**) (1.7 mmol) or *O*-aminothiophenol (1.7 mmol) (**4**), PEG-400 (5 vol.) and PTSA (30 mol %) was heated at 120 °C for 4 h (5 h for **5**). After completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature, diluted with aqueous Na_2CO_3 solution (10 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude **3** or **5**, which was further purified by column chromatography on silica gel using EtOAc/hexane as eluents.
*N-(1H-Benzo[d]imidazol-2-yl)benzamide (**3a**):* ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.13–7.15 (m, 2H), 7.45–7.48 (m, 2H), 7.53 (m, 2H), 7.61 (t, J = 7.2 Hz, 1H), 8.15 (d, J = 7.2 Hz, 2H), 12.25 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 113.1, 121.0, 122.6, 128.2, 128.3, 131.9, 134.4, 148.9, 168.9; HRMS m/z calcd for $C_{14}H_{11}N_3O$ $[M+H]^+$ 238.0980, found 238.0989.
*N-(Benzo[d]thiazol-2-yl)benzamide (**5a**):* ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.35 (t, J = 7.6 Hz, 1H), 7.48–7.58 (m, 3H), 7.66–7.69 (m, 1H), 7.79 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 2H), 12.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 120.2, 121.7, 123.6, 126.1, 128.2, 128.6, 131.5, 132.0, 132.8, 147.2, 158.5, 165.1; HRMS m/z calcd for $C_{14}H_{10}N_2OS$ $[M+H]^+$ 255.0592, found 255.0580.